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<p>(54) Title: GAS DRIVEN DRUG DELIVERY DEVICE</p> <div data-bbox="303 1121 1281 1675"> </div> <p>(57) Abstract</p> <p>A subcutaneous drug delivery device (10) comprises a housing having an internal reservoir (12) in communication with a drug delivery needle (21) via a fluid path (23). An expandable chamber (14) disposed adjacent to the reservoir (12) forces drug from the reservoir (12) to the needle (21) when supplied with a gas. A flow regulating chamber (24-26), in communication with the fluid path, is capable of volumetric changes in response to temperature and/or pressure changes. An increase in the volume of the flow regulating chamber (24-26) increases flow resistance to the needle (21) and thereby counteracts the corresponding increase in delivery rate resulting from the expansion of the expandable chamber (14) due to the same volumetric changes in response to temperature and/or pressure.</p>		

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Description

GAS DRIVEN DRUG DELIVERY DEVICE

Technical Field

5 This invention relates to a subcutaneous drug delivery device having an improved filling system.

Background Art

10 A wide range of subcutaneous drug delivery devices are known in which a drug is stored in an expandable-contractible reservoir, the drug being delivered from the reservoir by forcing the reservoir to contract. (The term "subcutaneous" as used herein includes subcutaneous, intradermal and intravenous.)

15 Such devices can be filled in the factory or can be filled by the pharmacist, physician or patient immediately prior to use. In the former case it may be difficult to provide the required drug stability in the device since the drug will be stored in the reservoir for a shelf life of from several months to a number of years. In the latter case, it is difficult to ensure that the drug has completely filled the reservoir, i.e. that the reservoir and fluid path do not contain any air bubbles. In general, this requires priming the device by filling it in a certain
20 orientation which ensures that the air bubbles are pushed ahead of the drug, such as with the filling inlet at the bottom and the delivery outlet at the top (to allow the bubbles of air to rise during filling).

25 The present invention aims to provide a subcutaneous drug delivery device having an improved filling mechanism which facilitates filling the device in an orientation-independent manner.

A further problem associated with subcutaneous drug delivery devices is that in many cases gas generation is used to compress the reservoir. While it may be possible to ensure a constant or a

controllably varying rate of gas generation (for example by passing a constant current through an electrolytic cell), this does not ensure a constant rate of drug delivery.

5 The amount of compression of the reservoir (and thus the rate of delivery of drug) depends on the amount by which the volume of the gas generation chamber expands. The behaviour of an ideal gas is governed by the equation $PV=nRT$, in which the volume of gas, V , is proportional to the number of moles of gas, n , and the temperature, T , and inversely proportional to the pressure, P .

10 An electrolytic cell working at constant current will generate a constant number of moles of gas *per* unit time. However, changes in the temperature of the gas and in the atmospheric pressure exerted on the gas will cause the volume to vary. Even if the temperature of the device remains constant, the fact that atmospheric pressure drops by
15 approximately 3% for every increase in altitude of 300m means that the delivery rate will vary substantially between a location at sea level and a higher altitude location (for example, Denver, Colorado is approximately 5 miles or 8 km above sea level, so atmospheric pressure will be approximately 15% lower on average than at sea
20 level). Similarly, normal changes in atmospheric pressure due to the weather cause the delivery rate of this type of device to vary.

It is thus an object of the present invention to provide a device which operates at a substantially constant delivery rate independently of the ambient atmospheric pressure.

25 A further object of the invention is to provide a device having improved adhesion to the skin, i.e. for which there is less likelihood that the device will become detached during use.

30 For devices which employ a needle to penetrate the skin there is a danger that after use the device may accidentally infect the patient or others if not properly disposed of. Our WO 95/13838 discloses an intradermal device of this type having a displaceable cover which is

moved between a first position in which the needle is retracted before use and a second position in which the needle is exposed during use. Removal of the device from the skin causes the cover to return to the first position in which the needle is again retracted before disposal.

5 The present invention aims to decrease the possibilities that the needle could become exposed by accident before or after use for example by a child playing with the device if not properly disposed of. Clearly given the risks associated with infectious diseases, particularly those carried by blood, any possibility of accidental infection must be
10 minimised to the utmost and preferably eliminated entirely.

 When filling a drug delivery device, the conventional method is to use a syringe, which carries the risk of accidental injury. The present invention has as a further aim the improvement of safety when syringes are used.

15 Our International Application No. PCT/IE 96/00059 discloses a medicament delivery device having a filling mechanism integral within the housing which receives a cylindrical cartridge (or "vial") sealed by a sliding stopper. When the cartridge is pushed into the filling
20 mechanism, a hollow needle in the filling mechanism penetrates the stopper and establishes communication between the interior of the cartridge and the device's internal reservoir. Continued movement of the cartridge into the filling mechanism causes the stopper to slide into the cartridge and act as a piston to pump the medicament from the
25 cartridge into the reservoir. While this mechanism overcomes some of the disadvantages of using a syringe, it also makes the device bulkier. The present invention has as a further object the provision of a less bulky non-syringe based filling mechanism.

 With both syringe- and cartridge-based filling mechanisms there is a difficulty in ensuring that the device has been filled with the
30 correct dose. The present invention further aims to provide a filling mechanism which facilitates loading a precise dose into the reservoir.

Disclosure of Invention

The invention provides drug delivery device comprising:

a housing having an internal reservoir and an expandable chamber disposed relative to the reservoir,

5 a drug delivery needle extending from the housing for penetration of the skin of a subject, the needle having an outlet for drug delivery,

a fluid path defined between the delivery needle outlet and the reservoir,

10 means for providing a gas at a controllable rate into said expandable chamber,

and a flow regulating chamber, in communication with the fluid path, which is capable of volumetric changes in response to temperature and/or pressure changes.

15 By calibrating the degree of increase or decrease in flow resistance, it is possible to compensate for differences occurring in the rate of delivery which arise because of pressure- or temperature-induced differences in the volume of a given mass of gas in the expandable chamber. Thus, if the ambient atmospheric pressure drops,
20 the gas in the expandable chamber will tend to expand and thereby force more drug from the reservoir. This will however be counteracted by the flow regulating chamber which will increase flow resistance along the fluid path and thereby counteract the increased flow rate arising from the effect of the tendency for the expandable
25 chamber to expand.

Preferably, the expandable chamber causes contraction of the reservoir in use.

Further, preferably, the flow regulating chamber alters the drug delivery rate by varying the flow resistance between the reservoir and
30 the outlet.

Preferably, the flow regulating chamber is associated with a blocking member which upon expansion of the flow regulating chamber moves within the fluid path so as to restrict the flow of drug.

5 Further, preferably, the blocking member comprises a formation provided on a displaceable member which at least partially bounds the flow regulating chamber, the formation being disposed adjacent to an inlet of a conduit forming part of said fluid path, such that restriction of the fluid path occurs when the blocking member is moved into the inlet of the conduit.

10 By having a suitably shaped and sized formation relative to the inlet, it is possible to precisely vary the flow resistance of the conduit, and thereby precisely control the delivery rate notwithstanding changes in ambient temperature and/or pressure.

15 Suitably, the shape of the blocking member is adapted to cut off the fluid path completely with a predetermined degree of expansion of the flow regulating chamber.

Alternatively, the formation can be shaped such that the fluid path is never entirely cut off.

20 In preferred embodiments of the invention, a displaceable cover is connected to the housing such that displacement of the housing relative to said cover when said cover has been applied to the skin of a subject causes the delivery needle to penetrate the skin of the subject.

25 Such a displaceable cover is suitable for concealing the needle before and after application to the skin of a subject, which prevents injury and reduces the possibility of contamination of the needle.

In another aspect of the invention the expandable chamber is provided with a release valve operatively connected to the displaceable cover such that the movement of the housing relative to the cover controls the closing of the valve and thereby the sealing of the

expandable chamber. This feature is not dependent on the existence of the flow regulating chamber.

5 The valve enables the device to be supplied with the displaceable member positioned such that the volume of the (empty) reservoir is minimised and that of the expandable chamber maximised. Thus, the reservoir can be of substantially zero volume initially, with no entrapped air volume. The device can then be primed or loaded by filling the reservoir, for example using a syringe- or cartridge-based filling mechanism.

10 As the reservoir is filled, the displaceable member moves to expand the reservoir and thereby contract the expandable chamber. The valve allows the air or other gas in the expandable chamber to be exhausted into the atmosphere.

15 The device can then be applied to the skin of the user. When the device is applied the housing moves relative to the cover which is applied to the skin, not only does the needle penetrate the skin, but also (because the valve is operatively connected to the cover) the valve is closed to seal the expandable chamber. If the valve remained open then gas supplied into the expandable chamber would be free to escape and
20 delivery would not be effected. While it would be possible for the user to close the valve manually, this would clearly leave open the possibility of error. Instead, by connecting the valve operatively to the cover, it is possible to ensure that the valve is always closed when the device is applied to the skin.

25 Preferably the valve comprises two components one of which is connected to the cover and the other of which is connected to the expandable chamber, such that relative movement of the housing towards the cover causes the valve to close.

30 When a displaceable cover is provided, a further aspect of the invention is that the displaceable cover is displaceable relative to the housing between a first position in which the needle is concealed from

the exterior of the device and a second position in which the delivery
needle protrudes from the device for penetration of the skin, the device
further comprising means for locking the device in the first position
after a single reciprocation of the device from the first position to the
5 second position and back to the first position.

This feature is in and of itself advantageous, since it addresses the
difficulties of prior art devices which, even when disposed of after use
with the needle concealed, can be activated to cause the needle to
protrude thereby giving rise to injury. According to the invention,
10 however, the locking means is engaged automatically when the cover
and housing are reciprocated relative to one another once, i.e. the
housing and cover are moved relative to one another to cause the
needle to protrude when the device is applied to the skin, and this
relative movement is reversed when the device is removed, thereby
15 concealing the needle but importantly, also engaging the locking means
to prevent the needle from being exposed again by accident.

Preferably, the locking means comprises a mechanical latch
which is brought into operation by said reciprocation.

Further, preferably, the latch comprises a pair of elements
20 mounted on the cover and the housing respectively, said elements being
shaped such that they can have two relative configurations when the
cover is in said first position relative to the housing, namely a movable
configuration in which the elements are mutually movable, and a
locked configuration in which the elements are prevented from mutual
25 movement, and wherein reciprocation of the cover and the housing
causes the elements to pass from the first movable configuration,
through an intermediate configuration when the cover is in said second
position relative to the housing, and then to said locked configuration,
thereby preventing any further movement of the cover relative to the
30 housing.

In preferred embodiments illustrated further below, one of said
elements is provided with a recess which is adapted to receive a

projection on the other of said elements, the recess and the projection being spaced apart from one another in the movable configuration, and being in engagement with one another in the locked configuration.

5 These embodiments are preferred because while they are mechanically simple and easy to make, their very simplicity provides fewer opportunities for malfunction.

Preferably, movement of the cover relative to the housing is initially prevented by a removable locking member.

10 This feature helps to prevent accidental injury occurring because the needle is only exposed when the housing is moved relative to the cover, i.e. only after the user has specifically removed the removable locking member.

Suitably, the presence of said removable locking member also prevents the means for providing a gas from being actuated.

15 This prevents the device from being exhausted by accidental switching on at an incorrect time.

Suitably, said removable locking member comprises a laminar member inserted between said cover and said housing.

20 In a further aspect of the invention, the surface of the housing from which the needle extends or the surface of the displaceable cover, if present, is of concave cross-section, such that when the device has been applied to the skin of a subject removal of the device is resisted because the cover conforms more closely to the skin.

25 In prior art devices, it has been found that retention on the skin of the user is problematic because of adhesive failure, for example. Using a concave surface causes the device to be retained more effectively by adhesive means.

With prior art devices the lower surface tends to be peeled away from the skin more easily as the edges of the device can be detached relatively easily. Where a concave lower surface is used the edges tend to remain in contact with the skin and removing the device is thus more difficult. In effect a shear force is required rather than a simple peeling, and this assists in preventing accidental removal. This feature is not dependent on the existence of the other aspects of the invention referred to above.

In a modified device according to the invention, the needle extends from the lower surface of the housing is replaced by a tube extending from the housing, said tube being adapted to carry a drug delivery needle thereon.

Such a device is preferred for intravenous delivery of a drug as the needle carried on the end of the tube can be accurately located in a suitable vein. The needle may be integral with the tube or supplied separately.

In a further preferred feature, the reservoir is separated from the expandable chamber by a diaphragm which exhibits bistable behaviour, such that in one stable state the reservoir is full and in the other stable state the reservoir is empty, the diaphragm being shaped to minimise the energy required in the transition between said stable states.

Preferably the diaphragm is in the form of a body having a peripheral lip connected to a substantially flat central section by a flexible annular section, said flexible annular section assuming a substantially frusto-conical cross-section in one of said states and assuming an arcuate curved cross-section in the other of said states.

Preferably, the means for providing a gas comprises an electrical circuit in which any transistors are bipolar transistors having a gain of not less than 500, such that said circuit can be irradiated by ionising radiation without destroying the circuit.

This type of transistor has been found to be advantageous as it enables the device to be sterilised using gamma radiation with the electronic components intact. While a certain loss of performance results from the irradiation, the high gain transistor still has an adequate gain after irradiation to operate reliably.

Further, preferably, the current gain of the or each transistor is not less than 750.

For example, a transistor having a rated current gain of 800 has been found to give an excellent performance after irradiation, despite the fact that irradiation lowers the current gain characteristics of the transistor by a factor of ten or more. The initial high gain compensates for the subsequent reduction arising from irradiation. The fact that the effects of irradiation can be predicted means that the performance after irradiation is reliable.

Further, preferably, the circuit further comprises a reference component across which a fixed potential drop is measurable, said reference component being essentially unchanged by said ionising radiation.

If a reference voltage is used which is not affected by the irradiation process, then the operation of the other components in the circuit may be determined by this reference voltage. For example, while the current gain of a group of transistors may vary individually when a batch is irradiated, each such transistor can be used to make an identically functioning amplifier if the output current of the amplifier is matched against a given reference component.

Advantageously, said reference component comprises a light-emitting diode.

Light emitting diodes (LEDs) have been found to be affected less than other standard components when irradiated by gamma radiation.

In a particularly preferred embodiment, said light emitting diode employs gallium arsenide as a semiconductor.

5 Gallium arsenide (GaAs) LEDs are virtually unaffected by gamma rays and thus make ideal reference components according to the invention.

In a further aspect, the invention provides a subcutaneous drug delivery kit comprising:

10 a) a device according to any preceding claim which is provided with a filling mechanism associated with the reservoir, the filling mechanism comprising means for receiving a filling adapter as defined in b), and

15 b) a filling adapter, comprising a body which is adapted to accommodate a cartridge, the body having means for engaging the adapter-receiving means of the device at one end thereof, means for receiving a cartridge at the other end thereof and transfer means for transferring a liquid from a cartridge to the filling mechanism of the device as the cartridge is emptied;

20 wherein the means for receiving the adapter provided on the device and the corresponding engaging means provided on the adapter together constitute a releasable locking mechanism which holds the adapter in place on the device once engaged, said locking mechanism being disengaged by the cartridge when the cartridge is emptied within the adapter.

25 The kit according to the invention is advantageous because it eliminates the need for a bulky filling mechanism which accommodates the cartridge within the device, and instead employs an adapter which is releasable from the device so as to enable the filled device to be less bulky than prior art cartridge-based devices.

Furthermore, the locking mechanism employed is only disengaged when the cartridge has been pushed fully home. If the cartridge used is of a type which will empty when pushed fully home, this feature ensures accurate loading of the reservoir, i.e. it is not possible to easily remove the device before the reservoir is filled with the correct dose of medicament.

Suitably, said transfer means comprises a hollow double-ended needle, one end of which is associated with the engaging means such that it communicates with the filling mechanism when the adapter is engaged with the device, and the other end of which is associated with the cartridge receiving means such that it communicates with the interior of a cartridge having a penetrable stopper when such a cartridge is received by the adapter.

Such a hollow double ended needle can be replaced by a pair of needles which are connected by a conduit, such as a moulded conduit running through the body of the adapter and having a needle mounted at either end such that it is functionally equivalent to a double ended needle.

Preferably, both ends of the needle are disposed within the body of the adapter such that they are recessed from the exterior of the body when the adapter is disengaged from the device.

For safety reasons, this arrangement is preferable, as it allows the adapter to be disposed of without fear of accidental injury occurring from casual handling of the adapter.

In a preferred embodiment, the releasable locking mechanism comprises a pair of locking members provided on the adapter receiving means and the corresponding engaging means, respectively, one of said locking members being movable between a locking position and a disengaging position, and said movable locking member being disposed relative to the body such that, in use, when a cartridge is emptied within the body, said movable locking member is moved from the

locking position to the disengaging position under the action of the cartridge.

For example, where a substantially cylindrical cartridge is employed, the body can receive the cartridge within a passage having a diameter sufficient to completely accommodate the cartridge, but with the end of the passage (only reached by the cartridge when the cartridge is pushed fully home) being of slightly narrower diameter on account of a projection provided on the movable locking member. Thus, when the cartridge is pushed fully home, it contacts the movable locking member and pushes it out of the way, thereby disengaging the locking mechanism.

Suitably, said movable locking member is resiliently biased towards the locking position.

Preferably, said movable locking member is a latch which automatically locks the adapter and device to one another when engaged together.

Further, preferably, the cartridge is emptied by moving the penetrable stopper against the adapter.

In a further aspect the invention provides a subcutaneous drug delivery kit comprising:

- a) a device according to any preceding claim further comprising a filling mechanism associated with the reservoir, the filling mechanism comprising means for receiving a filling adapter as defined in b), and
- b) a filling adapter, comprising a body which is adapted to receive a syringe, the body having means for engagement with the adapter-receiving means of the device at one end thereof, syringe-receiving means at the other end thereof and transfer means for transferring a liquid from the syringe to the filling

5 mechanism of the device as the syringe is emptied, said transfer means comprising a conduit associated with the syringe receiving means, the conduit leading to a needle which is associated with the engagement means and is disposed within the body of the filling adapter.

10 The adapter preferably receives the syringe without a needle being provided on the syringe. This fact, along with the fact that the needle on the adapter is recessed from the exterior of the adapter body means that a conventional syringe (minus needle) can be used to fill the device without any risk of accidental injury occurring.

Preferably, in such a kit, the needle is disposed within the body of the filling adapter such that it is recessed from the exterior of the body when the adapter is disengaged from the device. This helps to avoid accidental injury or infection occurring.

15 In a further aspect, the invention provides a method of filling a drug delivery device, comprising the steps of:

- 20 providing a drug delivery device having a drug reservoir, the reservoir being associated with a filling mechanism comprising filling adapter receiving means;
- providing a filling adapter having a first end for engagement with the adapter receiving means, and a second end for receiving a syringe;
- causing the filling adapter receiving means to receive the filling adapter;
- 25 causing the second end of the filling adapter to receive a syringe having liquid stored therein and a needle;
- providing a conduit for communication between the liquid stored within the syringe and the first end of the filling adapter; and
- 30 emptying the syringe and concurrently transferring the liquid from the syringe to the device *via* the conduit.

In yet further aspects, the invention provides a filling adapter as defined above and a diaphragm as defined above.

Brief Description of Drawings

5 The invention will be further illustrated by the following description of embodiments thereof, given by way of example only with reference to the accompanying drawings, in which:

Fig. 1 is a sectional side view of a first embodiment of drug delivery device according to the invention;

10 Fig. 2 is an exploded perspective view of the flow regulating chamber and needle assembly of the first embodiment of the device of Fig. 1;

Fig. 3 is an enlarged sectional side view of the flow regulating chamber and needle assembly of the first embodiment of the device of Fig. 1;

15 Figs. 4-6 are sectional side views of a second embodiment of drug delivery device according to the invention, shown before, during and after use, respectively;

20 Figs. 7-9 are enlarged perspective views of the locking mechanism of the device of Figs. 4-6, shown before, during and after use, respectively;

Fig. 10A, 10B and 10C are schematic elevations of a first alternative embodiment of a locking mechanism, shown before use, during use and after use, respectively;

25 Fig. 10D is a perspective view of the locking mechanism as shown in Fig. 10A;

Fig. 11A, 11B and 11C are schematic elevations of a second alternative embodiment of a locking mechanism, shown before use, during use and after use, respectively;

5 Fig. 11D is a perspective view of the locking mechanism as shown in Fig. 11A;

10 Fig. 12A, 12B and 12C are schematic elevations of a third alternative embodiment of a locking mechanism, shown before use, during use and after use, respectively;

Fig. 12D is a perspective view of the locking mechanism as shown in Fig. 12A;

15 Figs. 13A, 13B and 13C are schematic elevations of a fourth alternative embodiment of a locking mechanism, shown before use, during use and after use, respectively;

Fig. 13D is a side elevation of the locking mechanism as shown in Fig. 13A;

20 Fig. 13E is a perspective view of the locking mechanism as shown in Fig. 13A;

Figs. 14 and 15 are sectional elevations of a third embodiment of drug delivery device according to the invention, shown before and during use, respectively;

25 Fig. 16 is a partially cut away perspective view of the lower part of the housing on the third embodiment of the device of Figs. 14 and 15, including various components housed therein;

Fig. 17 is an exploded perspective view of the electrolytic cell used in the embodiment of Figs. 14 and 15;

Fig. 18 is a sectional side view of the electrolytic cell used in the embodiment of Figs. 14 and 15;

5 Figs. 19 and 20 are sectional side views of a fourth embodiment of drug delivery device according to the invention, shown before and during use, respectively;

10 Fig. 21 is a sectional plan view of a drug delivery kit comprising the first embodiment of Fig. 1, a filling adapter and a medicament cartridge;

Fig. 22 is a perspective view of a subassembly used in the adapter shown in Fig. 21;

15 Figs. 23 and 24 are sectional side views of the drug delivery kit of Fig. 21, shown during and after filling of the device, respectively;

Figs. 25 and 26 are sectional side views of fifth and sixth embodiments, respectively, of drug delivery device according to the invention;

20 Figs. 27 and 28 are sectional side views of a diaphragm suitable for use in a device according to the invention;

25 Fig. 29 is a diagram of an electronic controller circuit suitable for use in a device according to the invention; and

Figs. 30 and 31 are perspective views of the top side and underside, respectively, of a displaceable cover from a device according to the invention.

Mode for Carrying Out the Invention

5 In Fig. 1 there is indicated, generally at 10, a subcutaneous drug delivery device according to the invention. A housing 11 defines a reservoir 12 which is partially bounded by an elastomeric diaphragm 13 which allows the reservoir 12 to expand and contract. Diaphragm 13 also bounds an expandable chamber 14 such that expansion of the
10 expandable chamber 14 causes the reservoir 12 to contract and *vice versa*. In Fig. 1, reservoir 12 is at full volume and contains a drug, while expandable chamber 14 is at minimum volume.

 A circuit board 15 having an electrolytic cell mounted thereon (explained in greater detail below) is mounted in the lower part 16 of
15 housing 11. In use, the electrolytic cell feeds a gas in use into expandable chamber 14 *via* an aperture 17 in a supporting member 18.

 Reservoir 12 is provided with an inlet 19 which is in communication with a filling mechanism 20 (explained in greater detail below). A delivery needle 21 provided with an outlet 22 is in
20 communication with reservoir 12 *via* a fluid path 23 which is indicated by arrows. The fluid path 23 passes around an air-filled flow-regulating chamber which comprises a top member 24, annular member 25 and diaphragm 26. The fluid path also passes *via* a needle holder 27 to the needle 21. The inlet to the needle 21 is partially
25 restricted by a projection 28 on diaphragm 26, such that any upward movement of projection 28 reduces resistance to flow and any downward movement of projection 26 increases flow resistance.

 Referring additionally to Fig. 2, the flow regulating chamber can be seen in exploded view. Thus, top member 24, annular member 25
30 and diaphragm 26 can be seen. Annular member 25 accommodates diaphragm 26, and the three components 24,25,26 fit together to form

an airtight chamber which is positioned above needle holder 27. The inlet in needle holder 27 leading to needle 21 can be clearly seen on the top surface of needle holder 27. It is into this inlet that projection 28 (Fig. 1) extends.

5 Further features of device 10 which can be seen in Fig. 1 are a displaceable cover 29 attached to the housing 11 by a hinge 30. The movement of displaceable cover between the position shown in Fig. 1 (wherein the needle 21 protrudes through displaceable cover 29) and a position in which the needle 21 is substantially concealed by
10 displaceable cover 29(as shown in Fig. 4), is controlled by a locking mechanism indicated generally at 31 and explained in greater detail below.

Displaceable cover 29 which, in use, is affixed to the skin using an adhesive coating 29' provided on the surface thereof distal from the
15 housing ("the underside"). The displaceable cover 29 has a concave shape when viewed from the underside. This shape is advantageous because if a flat or convex surface is provided, the edges of the cover 29 will be more easily peeled away from the skin by accident, i.e. the use of a convex surface is less likely to have protruding edges, and the
20 force required to peel the device away is a shear force rather than a simple peeling force.

The housing 11 is covered by a protective top cover 32 which can provide a more aesthetically pleasing appearance to the device, as well as one which is ergonomically more advantageous for the user.
25 An aperture in protective top cover 32, indicated at 33, allows a transparent portion 34 of housing 11 to be seen, thereby allowing the user to visually check the reservoir to see whether drug is present.

The protective top cover 32 also protects the housing 11 and its component parts if the device 10 is mishandled or dropped

30 In Fig. 3, the flow regulating chamber is shown in greater detail. The chamber, indicated generally at 35, comprises top member 24,

annular member 25, and diaphragm 26, as explained above. The construction ensures that an airtight space 36 exists in the interior of chamber 35. A fluid path between the reservoir and the needle (Fig. 1) is shown with heavy arrows. As can be seen, projection 28 on
5 diaphragm 26 extends into the inlet 37 in needle holder 27 leading to the needle. The fluid thus has to push up on diaphragm 26 in order to reach the needle. Little force is required to do this, as the air in chamber 35 is compressible.

10 However, if the ambient atmospheric pressure drops, for example due to an increase in altitude, the fixed mass of air in chamber 35 tends to expand (since for ideal gases at fixed temperature the product of pressure and volume is a constant). This makes it more difficult for fluid to flow past diaphragm 26 into needle holder 27 and would thus tend to cause a decrease in the rate of delivery of drug.

15 The fact that the drug is being driven by a gas-filled expandable chamber, however, means that the expandable chamber tends also to increase in volume due to this increase in altitude, and the effect of an increase in expandable chamber volume is to speed up the rate of delivery.

20 Therefore, by calibrating the flow regulating chamber correctly, barometric changes which would otherwise tend to increase or decrease the rate of delivery of drug are counteracted by the corresponding increase or decrease in the amount of flow resistance exerted by the flow regulating chamber, thereby allowing a constant delivery rate to
25 be maintained.

It will be appreciated that changes in temperature which would cause the gas in the expandable chamber to expand or contract are also counteracted in the same way.

30 A further feature of the device of Figs. 1-3 is an o-ring 38 located on displaceable cover 29 (see Fig. 1). O-ring 38 forms a seal with needle holder 27 and thereby assists in protecting the puncture

point of the needle 21 into the skin of the user from contact with soap or water when the user takes a shower. If water contacts the needle 21, needle 21 may assist in water being drawn into the puncture by a wicking mechanism. However, adhesive 29' on displaceable cover 29 prevents water from reaching the needle *via* the underside of cover 29, and o-ring 38 prevents water from reaching the needle *via* the upper side of displaceable cover 29.

Figs. 4, 5 and 6 show a device similar to that of Fig. 1 before, during and after use, respectively. The device, indicated generally at 50, differs slightly from the Fig. 1 device and accordingly different reference numerals are used in relative to Fig. 1.

The device 50 is shown in Fig. 4 with the needle 51 concealed by the displaceable cover 52 because displaceable cover 52 is displaced relative to housing 53 about hinge 54. A removable tab 55 prevents displaceable cover 52 from being moved towards housing 53, as will be described further below. The underside 56 of displaceable cover 52 is coated with a contact adhesive, and during storage, the adhesive is protected by a release liner (not shown).

When the release liner is removed, the adhesive-coated underside 56 is pressed against the skin to ensure good adhesion (the concave surface assists in obtaining good adhesion) and the tab 55 is removed. The housing 53 is then pushed towards the skin and the needle 51 penetrates the skin as the displaceable cover 52 and housing 53 move together about hinge 54, leading to the configuration shown in Fig. 5.

A start button (not shown) is pressed to activate the gas generating electrolytic cell 57 (see Fig. 5). As gas is generated, a diaphragm 58 is pushed upwards to drive a liquid drug from reservoir 59 (which was filled before use *via* inlet 60) and thereby force the medicament through a fluid path 61 around flow regulating chamber 62 (as explained above in relation to Figs. 1-3) and to the patient *via* delivery needle 51.

When delivery has been completed, the diaphragm 58 will have moved up such that the space occupied by the reservoir 59 at the beginning of delivery (see Figs. 4 and 5) is now occupied by the expandable chamber 60 (see Fig. 6), since the expansion of the expandable chamber causes contraction of the reservoir.

The device 50 is removed from the skin by pulling upwards on upper protective cover 63 (Fig. 6) causing the needle 51 to be retracted behind displaceable cover 52 once again because the adhesive force holding the displaceable cover 52 against the skin is greater than the force exerted by the locking mechanism 64 (explained in greater detail below). Once the needle 51 is retracted in this way, the locking mechanism 64 holds the displaceable cover 52 permanently in the position shown in Fig. 6, i.e. away from the housing 53 with the needle 51 concealed.

Fig. 7 shows locking mechanism 64 in greater detail, with the protective top cover 63 removed for illustrative purposes. The locking mechanism 64 is illustrated before use, i.e. when the displaceable cover is positioned as shown in Fig. 4. In other words, there is a gap between the housing 53 and the displaceable cover 52 and the needle 51 (Fig. 4) is recessed in this gap and thereby concealed by the displaceable cover 52.

A projection 65 mounted on the front of housing 53 is positioned at the upper end of a slot 66. Slot 66 has an enlarged portion 67 at the lower end and is provided with wedge projections 68,69 at the exterior surface of the upper portion thereof. Slot 66 is formed in a member 70 which is attached to displaceable cover 52 by connecting arms 72 which allow a slight degree of flexibility.

A widened rib (not shown in Fig. 7) is provided on the projection 65, and the width of this rib is greater than that of the upper portion of the slot 66. The member 70 is biased slightly against this rib.

The removable tab (see Fig. 4) is positioned so as to engage wings 71 and prevent them from moving towards the cover 52. This effectively prevents the entire housing from being moved towards the cover and prevents the device from being activated. When the tab is removed, as shown in Fig. 7, the displaceable cover 52 can be snapped towards the housing 53 by pressing down on the housing. This results in the locking mechanism adopting the configuration shown in Fig. 8, wherein the projection 65 has moved to the lower end of slot 66, allowing the lipped member 73 to pass through the enlarged portion 67 at the lower end of slot 66. This allows member 70, which was biased in the direction of projection 65, to relax. The sides of lipped member 73 rest against member 70

When delivery is complete and the housing 53 is lifted away from displaceable cover 52, this disengages the lips of lipped member 73 from resting against member 70 and again moves projection 65 to the upper end of slot 66. However, lipped member 73 passes over the wedge projections 68,69, as shown in Fig. 9. When this happens, the wedge projections 68,69 catch the rib 73 and prevent it from moving back down. This effectively locks the locking mechanism 64 permanently in the configuration shown in Fig. 9, thereby concealing the needle 51 permanently from view and making the device 50 safe to dispose of.

An additional feature of the device of Figs. 4-8 relative to that of Fig. 1 can be seen with reference to Figs. 4-6. A pair of projections 74 grip the flow regulating chamber 62 before use to block the path between reservoir 59 and needle 51 before use (Fig. 4). When gas generation begins, the pressure of liquid in the reservoir 59 forces flow regulating chamber 62 downwards relative to the projections 74. The projections 74 are resilient and move together when flow regulating chamber 62 moves downwards. In this position the projections 74 hold flow regulating chamber 62 in a fixed position both during delivery (Fig. 5), and when the device is removed from the skin (Fig. 6). Thus, after delivery, accidental leakage of medicament from the needle (e.g.

due to gravity) is prevented by the fixed position of the flow regulating chamber 62.

5 A further feature of the embodiment of Figs. 4-6 is an annular elastomeric inwardly extending lip 75 which seals the skin at the point of entry of the needle 51 in the same manner as the o-ring 38 in the Fig. 1 embodiment, and thereby reduces the danger of infection due to wicking by the needle of substances into the skin.

10 Four alternative embodiments of different locking mechanisms according to the invention are shown in Figs. 10A-10D, 11A-11D, 12A-12D, and 13A-13E. In each case the mechanism is shown schematically in "pre-use" (A), "in-use" (B) and "post-use" (C) configurations as well as in one or two perspective views (D/E). The mechanism can in each case be moved from position A to position B and from position B to position C with little difficulty (although 15 generally some resistance is present to prevent spontaneous or accidental movement), but once in position C, the mechanism is effectively locked permanently and is no longer capable of operation.

The first alternative embodiment of a locking mechanism comprises a resilient arm and related assembly and is shown in Figs 20 10A-10D. In Fig. 10A the locking mechanism is indicated generally at 80 and comprises a biasing member 81 and a resilient strut 82 mounted on the housing 83, and the resilient arm 84 and a post 85 mounted on the displaceable cover 86.

25 The resilient arm 84 is flexibly hinged at the base thereof 87. When housing 83 is pushed towards displaceable cover 86, biasing member 81 pushes the resilient arm 84 against the post 85. The resilient arm 84 and post 85 are mutually shaped to allow the arm 84 to pass over the top of the post 85, where it latches (see Fig. 10B) and is prevented from returning to the position shown in Fig. 10A.

30 In passing over the top of the post 85, the arm 84 acts against the resilient strut 82, momentarily bending the strut 82 away from the

biasing member 81, although when the arm 84 has passed fully over the top of the post 85 the strut 82 has returned to its relaxed (straight) position (Fig. 10B).

5 When (after use) the housing 83 is pulled away from the displaceable cover 86, this causes the strut 82 to again be bent away from biasing member 81 (because arm 84 which is now locked in place by post 85 impedes the path of strut 82). However, when the end 88 of strut 82 has cleared the arm 84, it springs back into position, past a projection 89 on arm 84 (see Fig. 10C). In fact, strut 82 latches behind
10 projection 89, preventing the strut from moving back to the position shown in Fig. 10B, and thereby permanently locking the mechanism 80 in the Fig. 10C configuration.

 The perspective view in Fig. 10D shows the mechanism in the position illustrated in Fig. 10A. An additional feature visible in Fig.
15 10D is a snap mechanism comprising an arm 90 depending from either side of the housing 83. A raised protuberance 91 on the inner surface of each arm 90 acts against a sloped surface 92 on the displaceable cover 86 to provide resistance to movement. The effect of the snap mechanism is to add further resistance to any unintended relative
20 movement between the housing 83 and the displaceable cover 86. A further effect is that the movement of the housing relative to the cover between the configurations of Figs 10A and 10B, and the configurations of Figs 10B and 10C, is extremely rapid, causing the penetration of the needle into the skin and the removal of the needle
25 from the skin to be quick and painless.

 The second alternative embodiment of a locking mechanism of the present invention comprises an inverted V-shaped assembly and is shown in Figs 11A-11D. In Fig. 11A the locking mechanism is indicated generally at 100 and comprises a member 101 resiliently
30 mounted on housing 102, and a pin 103 supported in a frame 104 mounted on displaceable cover 105. Member 101 defining a slot 106 therein of the generally inverted V-shape such that it has an outer slot portion 107 connected at the upper end thereof to an inner slot portion

108, and a dividing member 109 between the outer and inner slot portions 107, 108 below the upper ends.

5 In moving from the "pre-use" position to the "in-use" position, the (fixed) pin 103 moves up outer slot 107, acting against dividing member 109 until it springs past dividing member 109 at the top of the outer slot. In the position shown in Fig. 11B, the pin 103 is located above the top of the inner slot 108.

10 When the housing 102 is subsequently pulled away from the displaceable cover 105 (moving from Fig. 11B to Fig. 11C, the pin moves down inner slot 108, acting against the dividing member 109 to push member 101 sideways. When the position shown in Fig. 11C is reached, pin 103 locates a recess 110 (see Fig. 11B) in the lower end of inner slot 108, which allows the member 101 to relax slightly but still keeping a certain degree of stress on member 101 by holding it away from the equilibrium position relative to the housing 102. In this way, pin 103 latches into recess 110 and locks the mechanism 100 permanently in the "post-use" configuration.

15 In Fig. 11D, the mechanism 100 can be seen in the "pre-use" configuration, with member 101, housing 102, pin 103, frame 104, and displaceable cover 105 visible.

20 The third alternative embodiment of a locking mechanism of the present invention comprises generally a rotatable pawl assembly and is shown in Figs. 12A-12D. The mechanism, indicated generally at 120, comprises a rotatable pawl 121 mounted on the displaceable cover 122 and which is rotated by an arm 123 in moving from the "pre-use" to "in-use" positions (Figs. 12A and 12B, respectively). When the rotatable pawl 121 reaches the "in-use" position, a recess 124 (Fig. 12A) receives a projection 125 located on a resilient portion 126 of displaceable cover 122, providing a degree of resistance to further movement.

In moving from the Fig 12A to 12B positions, rotatable pawl 121 acts against a flexible strut 127 depending from housing 128. When the rotatable pawl 121 is in the Fig. 12B position, further clockwise rotation of the pawl is prevented by arm 123.

5 When the housing 128 is lifted (moving from Fig. 12B to 12C), strut 127 acts against a projection 129 urging the rotatable member 121 in a clockwise direction, but arm 123 prevents such rotation. As the housing reaches the Fig. 12C position, strut 127 springs past projection 129 to sit in a recess above projection 129, and arm 123 clears the
10 upper corner of rotatable pawl 121. When in this configuration, arm 123 prevents any counter-clockwise rotation of the rotatable pawl 121, while strut 127 prevents any clockwise rotation thereby locking the rotatable pawl 121 in position and preventing any further downward movement of housing 128 towards displaceable cover 122.

15 The fourth alternative embodiment of a locking mechanism of the present invention comprises generally a flexible post assembly as shown in Figs. 13A-13E. In Fig. 13A the locking mechanism is indicated generally at 130 and comprises a vertical flexible post 131 (see Figs. 13D and 13E) mounted on the displaceable cover 132 and
20 having a projection 133 extending therefrom towards a sloped surface 134 on the housing 135.

A slot 136 in surface 134 connects two apertures, namely a lower aperture 137 (see Fig. 13B) which is of smaller diameter than the widest part of projection 133, and an upper aperture 138 which is of
25 larger diameter than the widest part of projection 133.

In the "pre-use" position, projection 133 is positioned at the lower aperture. As the housing moves towards the "in-use" position (Fig. 13B) the flexible arm 131 is bent back until projection 133 reaches the upper aperture 138 whereupon it springs back into position
30 as projection 133 moves through the upper aperture 138.

In moving to the "post-use" position, projection 133 is constrained by the slot 136 and arm 131 is bent forward until projection 133 reaches lower aperture 137 which provides a recess for projection 133 to spring back into (but not through). Because arm 131 remains bent forward slightly, this effectively traps projection 133 in lower aperture 137 and thereby holds the mechanism permanently in the "post-use" configuration, as shown in Fig. 13C.

In Fig. 14 there is indicated, generally at 140, another drug delivery device according to the invention similar in many respects to the embodiments previously described. Device 140 has a protective upper cover 141, housing 142, displaceable cover 143, delivery needle 144, flow regulating chamber 145 and three position locking mechanism 146.

The internal space of the embodiment of Fig. 14 defines an expandable chamber 147 when the diaphragm 148 is in the position shown or a reservoir when the diaphragm is in the position shown in dotted outline at 149. The expandable chamber 147 is initially air filled (Fig. 14 shows the device in the pre-use configuration before medicament has been loaded). Thus, the reservoir is substantially of zero volume. Expandable chamber 147 communicates with the atmosphere via an open valve 150.

When medicament is loaded into the reservoir *via* a fill port (not shown), the diaphragm moves downwards to position 149, with the reservoir filling with air and the expandable chamber 147 being emptied as the volume thereof decreases. Because the expandable chamber is in communication with the atmosphere, the air initially filling space 147 is exhausted into the atmosphere *via* the valve 150 without any necessity for action on the part of the user.

Furthermore, because the reservoir is initially of substantially zero volume, it does not require filling in any particular orientation. While prior art devices have required careful loading in order to ensure that all air bubbles are vented from the drug supply before

delivery begins, the only air in the drug path of the device of Fig. 14 is in the short, narrow portion of the device between the reservoir and the needle 144. Thus, when drug enters the reservoir it immediately pushes the small amount of air ahead of it through the narrow space towards the needle 144, irrespective of the orientation of the device 140. By filling with the drug until a drop of the drug appears on the end of the needle one can be sure that no air remains in the fluid path.

When the device 140 has been filled with drug, the diaphragm 148 is at the position shown at 149, and the valve 150 is open. However, when the displaceable cover 143 is applied to the skin, and the housing is pushed downwards, the valve 150 is closed and the closing of the valve actuates a switch 151 to begin generation of gas by an electrolytic cell 152 (described in more detail below).

The device 140 is then in the "in-use" position shown in Fig. 15, with reservoir 147 filled with drug, the diaphragm 148 in position 149, valve 150 and switch 151 closed, and electrolytic cell 152 actuated to generate a gas and hence begin delivery of drug from reservoir 147 to the patient through delivery needle 144.

Valve 150 is closed by a connecting member 153 which is connected to displaceable cover 143. When displaceable cover 154 moves towards housing 142, connecting member 153 fits into valve 150 and pushes it home to seal the expandable chamber 147 (the area below diaphragm 149) from the atmosphere. When a gas is generated by the electrolytic cell 152, it pressurises the expandable chamber 147.

A coloured plastics member 154 forming part of locking mechanism 146 protrudes through an aperture 155 in protective upper cover 141 when the device is in the position as shown in Fig. 15. The coloured member 154 visually indicates that the device has been actuated.

Fig. 16 is a detail view of the lower section 156 of the housing 142 (see Fig. 15). Lower section 156 houses a battery 157 and an

electrolytic cell 158, both mounted on a printed circuit board (PCB) 159. PCB 159 can be provided with controlling circuitry as required in order, for example, to vary the rate of delivery, stop delivery if the rate of gas generation is too high, or control the operation of the device 140 in any other way required. In the embodiment shown, the device is a disposable single-rate device which does not require advanced controlling circuitry, but more sophisticated devices are of course within the scope of the invention.

A cylindrical outlet 160 is formed in section 156, and this provides a valve seating for valve 150. When valve 150 is pushed upwards into outlet 160 it makes an airtight seal, as shown in Fig. 15. Recess 161 in valve 150 tightly accommodates connecting member 153 (Fig. 15), and the force used to push housing 142 down onto displaceable cover 143 as described above is sufficient to jam connecting member 153 in valve 150. This design enables the device to be removed from the skin by pulling housing 142 away from displaceable cover 143 to the "post-use" position, causing connecting member 153 (which is permanently mounted on displaceable cover 143 and at this stage jammed into valve 150 also) to pull the valve 150 down and out of outlet 160 so as to open the valve. Using this design, if the reservoir is not empty when the device is removed, and if gas generation continues, then the gas will escape through outlet 160 rather than driving further medicament through the needle.

As described above, when valve 150 is closed it actuates a switch 151 (see Fig. 15) which comprises a fixed contact 162 and a rocking contact 163. This completes a circuit to connect battery 157 to electrolytic cell 158. When valve 150 is pulled downwards as the device is removed from the skin, the switch should automatically disconnect because of the resilience of rocking contact 163 which pivots about a fulcrum 164. Thus, the opening of the valve 150 is generally a redundant feature and is important as a safety feature if the switch does not automatically disconnect (leading to an unwanted continuation of delivery or, if the reservoir is already empty, to a build up of gas pressure inside the device).

The electrolytic cell 158 comprises (see also Figs. 17 and 18) a body 165 defining an internal space 166 for an electrolyte and through which a pair of electrodes 167 pass, each electrode being connected to a terminal of battery 157 (Fig. 16).

5 The internal space 166 is enclosed above and below by a pair of hydrophobic filters 168,169. These filters 168,169 retain the electrolyte but allow gas generated in the cell 158 to be released to the expandable chamber 147. The body 165 is provided with a seating 170 above and below, into which the filters 168,169 fit and are sealed in
10 place.

 The cell 158 is then sealed above and below by aluminium foil layers 171,172. A connecting cell 174 sealed at both ends by foil layers 171,172 enables gas passing through the hydrophobic filters 168,169 to be released, once the top foil layer 171 has been pierced. A gap
15 adjacent to the seating 170,171 enables gas escaping through hydrophobic filters 168,169 to reach the connecting cell 174. The foil layer 171 is pierced by a spike 175 carried on rocking contact 164 (see Fig. 16). Thus, when the device is actuated, foil layer 171 is pierced to unseal the cell 158. A hydrophobic filter 176 (see Fig. 17) is also
20 carried in the body 165 to enable the cell 158 to be filled with electrolyte by injection.

 In Figs. 19 and 20, a further embodiment 180 of the invention is shown. This embodiment differs from the embodiment of Figs. 14-18 only in that the valve member 181 is not held by the displaceable cover
25 182 when the device 180 is removed from the skin after use. However, the valve 181 nevertheless achieves the primary purpose of allowing the internal space 183 to be occupied entirely by the expandable chamber when received by the user, with the diaphragm 184 moving to the position shown at 185 when the device 180 is loaded with
30 medicament, which means that no air bubbles can be entrapped in the reservoir during filling, and the reservoir can thus be filled quickly and easily. The valve 181 closes automatically when the housing 186 is pressed towards the displaceable cover 182 (see Fig. 20).

Fig. 21 shows a device 190 according to the invention which is identical to the device of Fig. 1, together with a filling adapter 191 and a drug-containing cartridge 192. Cartridge 192 is cylindrical in shape, closed at one end 193 thereof and sealed at the other end 194 by an elastomeric stopper 195 which is fittably mounted in the cartridge 192. Because the cartridge's liquid-filled internal space 196 is sealed, the stopper 195 is prevented by the incompressible nature of the liquid from moving in either direction.

The adapter 191 comprises a housing 197 in which a cannula subassembly 198 is mounted. The subassembly 198 (see Fig. 22) comprises a plastic body 199 moulded in two halves 200,201, which when assembled together clamp a double-ended hollow needle or cannula 202 in place.

Device 190 is provided with a socket 203 for receiving adapter 191. A cylindrical projection 204 on the end of adapter 191 is designed to fit into socket 203, and also to conceal cannula 202 to prevent injury before and after adapter 191 is mounted on device 190. A self-sealing penetrable plug 205 mounted in socket 203 leads to a conduit 206 and an inlet for the reservoir (see inlet 19 in Fig. 1).

Subassembly 198 is mounted in a channel 207 of adapter 191 such that it can be pushed inward until a shoulder 208 meets the end of the structure 209 defining channel 207. At this point the cannula 202 will penetrate self-sealing member 205 enabling communication between cannula 202 and the reservoir of device 190.

In use, cartridge 192 is pushed into adapter 191, whereby stopper 195 causes subassembly 198 to be pushed inwards and cannula 202 to penetrate self-sealing member 205. Since the subassembly can move no further inward, further pushing of the cartridge into the adapter causes cannula 202 to penetrate stopper 195, thus putting drug-filled space 196 in indirect communication with the reservoir of device 190.

Since the stopper 195 is then held by subassembly 198, further pushing of the cartridge 192 inwards causes the stopper 195 (which remains stationary) to move relative to the cartridge 192 (which is progressively accommodated in the interior of adapter 191), with a consequent emptying of the contents of the cartridge 192 through the cannula 202 into the reservoir of device 190.

This is illustrated best in Fig. 23, which shows a sectional elevation of the components shown in sectional plan view in Fig. 21, after the cartridge 192 has been pushed most of the way home into adapter 191. It can be seen that at this point, stopper 195 (penetrated by cannula 202 which also penetrates self-sealing member 205) has almost reached the end 203 of cartridge 192.

Adapter 191 is not only held by the fit of projection 204 into socket 203, but also by a releasable locking mechanism 210 comprising an aperture 211 on device 190 and a resilient catch 212 on adapter 191 which is biased into the position shown in Fig. 23 so as to hold adapter firmly in place on device 190. Preferably the adapter and the device are sold together in kit form, optionally with the adapter already mounted on the device.

When cartridge 192 is pushed fully home it acts on a sloped section 213 of wall 214 of adapter 191 so as to push resilient catch 212, which is an extension of wall 214 downwards and thereby disengage locking mechanism 210, allowing adapter 191 to be removed from device 190.

Fig. 24 shows the kit after cartridge 192 has disengaged catch 212 allowing it to be withdrawn from aperture 211. This permits adapter 191 to be removed from device 190 by pulling projection 204 from socket 203 whereupon self-sealing member 205 seals itself and thereby isolates the reservoir of the device.

Because catch 212 is only disengaged when cartridge 192 is fully emptied (i.e. pushed fully home), one can ensure that the reservoir is

loaded with exactly the correct amount of drug every time, thereby eliminating human error and making the kit more suitable for home administration.

5 Furthermore, because both ends of cannula 202 at all times are concealed, the adapter 191 can be safely disposed of without risk of injury. The adapter 191 allows the drug to be transferred to the reservoir with sterility ensured, since the user does not at any time have to handle any of the components in the fluid path.

10 Fig. 25 shows a device according to the invention, indicated generally at 220, which differs from previous embodiments primarily in that instead of a needle extending directly from the housing 221, a tube 222 extends from the housing 221 and carries a connector 223 thereon to which a needle may be affixed before use. This device is particularly suitable for intravenous drug delivery because the tube 222
15 allows the needle to be accurately positioned in a vein.

Fig. 26 shows an alternative intravenous embodiment, indicated generally at 230. In this embodiment the displaceable lower cover has been omitted and the device is actuated by a contact switch 231 positioned on the underside of the housing 232. When the device is
20 applied to the skin, switch 231 is pressed inwards (to the position shown in Fig. 26), thereby closing an electrical circuit and actuating a gas generating electrolytic cell 233 in the manner previously described. As the snap action provided by previously described devices is not required to cause a needle to penetrate the skin, the cover can be
25 omitted without interfering with other functions of the device.

Fig. 27 shows the elastomeric diaphragm, indicated generally at 240, utilised in the above-described devices according to the invention. Diaphragm 240 can also be used in other drug delivery devices according to the invention. Diaphragm 240 is shown in Fig. 27 in its
30 relaxed position, as it would be when the reservoir is empty (see Fig. 6, for example). In this configuration the diaphragm 240 substantially has the form of a truncated cone having a sloped portion 241 surrounding a

flat portion 242, with a lip 243 surrounding sloped portion 241 (lip 243 is used to attach diaphragm 240 to the housing of a drug delivery device).

5 Fig. 28 shows diaphragm 240 in the configuration in which the reservoir is full (see Fig. 1, for example). In this configuration, the central portion 242 is still flat, and the surrounding portion 241 has an arcuate curved cross-section, in the form of a substantially inverted U shape.

10 The diaphragm 240 is bistable, such that it is stable in either the Fig. 27 or the Fig. 28 configuration. However, a particular advantage has been found to result from the fact that in moving from the reservoir full (Fig. 28) configuration to the reservoir empty (Fig. 27) configuration, very little energy is needed.

15 Unlike many bistable arrangements, only minimal force is required to move between the stable configurations. In many bistable arrangements a substantial amount of energy is required to move from one configuration to a midpoint, at which the amount of stored energy is relatively high, following which the stored energy is released to complete the transition. The diaphragm 240, rather than flipping
20 between configurations, makes a smooth transition. However, in contrast to a completely pliable body, which cannot be depended on to exert force uniformly, the diaphragm 240 will behave dependably since it is constrained in its movement between configurations.

25 In particular, this means that a predictable manner of movement is combined with a minimal expenditure of energy in actually effecting the transition between bistable configurations.

30 Fig. 29 shows a circuit diagram of a controlling circuit particularly useful for a drug delivery device according to the invention. In the circuit, indicated generally at 250, all symbols have their normal meanings within the art. The components shown are battery B1, switch S1 (activated by applying the device to the body),

fixed resistors R1-R6 and R9-R10, variable resistors R7 and R8, capacitor C1, transistors Q2-Q6, measurement terminals TP1 and TP2, light emitting diode LED, and load U1 which represents the electrolytic cell or other gas generating means.

- 5 Reference numeral 251 denotes a section of the circuit 250 which functions as a current driver, and reference numeral 252 denotes a section of the circuit 250 which functions as an error circuit.

10 The current through the electrolytic cell U1 determines the potential drop across variable the resistance comprising resistors R7 and R8 (which may be adjusted to calibrate the device or set the delivery rate). This potential drop is compared by the error circuit with the potential drop across a reference resistor R1, which itself depends on the voltage drop across the LED. The value of resistor R1 is chosen to provide a potential drop equal to the drop measured across
15 R7 and R8 when the correct current is flowing through cell U1.

 If the potential drop across R7 and R8 is lower than the constant potential measured across R1, indicating that the current through cell U1 is too low (e.g. because of fading battery power, changes in the internal resistance of electrolytic cell U1 as the reactants are consumed,
20 etc.), the error circuit 252 forces the driver 251 to increase the current flow to the correct value. In practice, the error circuit continually ensures that the current does not deviate from the correct value by constant feedback operation.

 Each of the transistors in the circuit 250 is a silicon-based
25 bipolar transistor. The advantage of using bipolar transistors in particular is that they have been surprisingly discovered to withstand gamma radiation to a far greater extent than other types of transistors. The use of silicon as semiconductor is not essential but this material is currently less expensive than many other semiconductors. It has been
30 found that by employing a circuit in which the or each transistor is a bipolar transistor, the circuit and hence the entire device can be subjected to intense gamma irradiation as a means of sterilising the

device after manufacture. Conventional integrated circuits are destroyed by the intense radiation required to sterilise a device quickly.

5 For example, a dose of 2.5 Mrad (25 kJ/kg) of gamma radiation may be required to sterilise a device. In trying to design a circuit which would withstand such harsh conditions we consulted data regarding the electronic components used in space missions, such as the U.S. Space Shuttle missions. It was found that the same degree of radiation resistance was not required because the absorbed dose measured on the Space Shuttle averages approximately 0.4-0.5 Mrad.

10 As a rule, all electronic components will undergo a degree of degradation when subjected to irradiation. However, by selecting components which are resistant to irradiation as far as possible and whose performance can be predicted after receiving a given dose of radiation, it is possible to design a circuit which will withstand intense gamma radiation and still function in a predictable manner.

15 In particular, by using a bipolar transistor with a high current gain (e.g. a current gain of at least 600 but preferably 800 or more) the drop in current gain exhibited after irradiation can be compensated for in advance. This drop in gain can be of the order of a tenfold drop or more, but can be predicted well in advance. Furthermore, by using current values which are sufficiently low the drop in voltage at the silicon junction of the transistor occurring as a result of the irradiation only slightly affects performance.

20 Yet a further advantage is gained using a circuit which employs a light emitting diode as a basis for the reference voltage used in the error correction circuit, since the LED reference source is not affected by the gamma radiation. The LED used is a gallium arsenide (GaAs) based LED which has been found to provide particularly good resistance to gamma radiation.

30 In summary, the components and circuit employed have been found to be suitable for gamma irradiation, following which they give

a well predictable performance in use. This enables the manufacture to be completed more efficiently, with the assembled device sterilisable by gamma radiation.

5 Fig. 30 is a perspective view of the top side of a displaceable cover 160 forming part of a device according to the invention. Fig. 31 is a perspective view of the underside of cover 160. Such a cover is described generally above in relation to the embodiment of Figs. 4-8, for example.

10 The cover 160 is provided with formations 161 forming part of a locking mechanism as described above, with an aperture 162 through which a delivery needle protrudes in use, and with hinge formations 163 which enable the cover 160 to be displaced relative to the housing between first and second positions as previously described.

15 The cover 160 is shaped to improve retention of the device against the skin: thus the top side 164 (Fig. 30) is convex, and the underside 165 (Fig. 31) from which the needle protrudes in use is concave. Accordingly, when the device has been applied to the skin of a subject removal of the device is resisted because the cover 160 conforms more closely to the skin. It is less likely that the device will
20 peel from the skin without a conscious effort by the user since there is a lower likelihood of the periphery of the cover being detached from the skin.

25 It should be understood that the foregoing relates only to preferred embodiments of the present invention and that numerous modifications or alterations may be made therein without departing from the spirit and scope of the invention as set forth in the appended claims.

Claims: -

1. A subcutaneous drug delivery device comprising:
 - a housing having an internal reservoir and an expandable chamber disposed relative to the reservoir,
 - 5 a drug delivery needle extending from the housing for penetration of the skin of a subject, the needle having an outlet for drug delivery,
 - a fluid path defined between the delivery needle outlet and the reservoir,
 - 10 means for providing a gas at a controllable rate into said expandable chamber,
 - and a flow regulating chamber, in communication with the fluid path, which is capable of volumetric changes in response to temperature and/or pressure changes.
- 15 2. A device according to Claim 1, wherein the expandable chamber causes contraction of the reservoir in use.
3. A device according to Claim 1 or 2, wherein the flow regulating chamber alters the drug delivery rate by varying the flow resistance between the reservoir and the outlet.
- 20 4. A device according to any preceding claim, wherein the flow regulating chamber is associated with a blocking member which upon expansion of the flow regulating chamber moves within the fluid path so as to restrict the flow of drug.
- 25 5. A device according to Claim 4, wherein the blocking member comprises a formation provided on a displaceable member which at least partially bounds the flow regulating chamber, the formation being disposed adjacent to an inlet of a conduit forming part of said fluid path, such that restriction of the fluid path occurs when the blocking member is moved into the inlet of the conduit.

6. A device according to Claim 4 or 5, wherein the shape of the blocking member is adapted to cut off the fluid path completely with a predetermined degree of expansion of the flow regulating chamber.
- 5 7. A device according to any preceding claim, wherein a displaceable cover is connected to the housing such that displacement of the housing relative to said cover when said cover has been applied to the skin of a subject causes the delivery needle to penetrate the skin of the subject.
- 10 8. A device according to Claim 7, wherein the expandable chamber is provided with a release valve operatively connected to the displaceable cover such that the movement of the housing relative to the cover controls the closing of the valve and thereby the sealing of the expandable chamber.
- 15 9. A device according to Claim 8, wherein the valve comprises two components one of which is connected to the cover and the other of which is connected to the expandable chamber, such that relative movement of the housing towards the cover causes the valve to close.
- 20 10. A device according to any one of Claims 7-9, wherein the displaceable cover is displaceable relative to the housing between a first position in which the needle is concealed from the exterior of the device and a second position in which the delivery needle protrudes from the device for penetration of the skin, the device further
- 25 comprising means for locking the device in the first position after a single reciprocation of the device from the first position to the second position and back to the first position.
- 30 11. A device according to Claim 10, wherein the locking means comprises a mechanical latch which is brought into operation by said reciprocation.

12. A device according to Claim 11, wherein said latch comprises a pair of elements mounted on the cover and the housing respectively, said elements being shaped such that they can have two relative configurations when the cover is in said first position relative to the housing, namely a movable configuration in which the elements are mutually movable, and a locked configuration in which the elements are prevented from mutual movement, and wherein reciprocation of the cover and the housing causes the elements to pass from the first movable configuration, through an intermediate configuration when the cover is in said second position relative to the housing, and then to said locked configuration, thereby preventing any further movement of the cover relative to the housing.

13. A device according to Claim 12, wherein one of said elements is provided with a recess which is adapted to receive a projection on the other of said elements, the recess and the projection being spaced apart from one another in the movable configuration, and being in engagement with one another in the locked configuration.

14. A device according to any one of Claims 7-13, wherein movement of the cover relative to the housing is initially prevented by a removable locking member.

15. A device according to Claim 14, wherein the presence of said removable locking member also prevents the means for providing a gas from being actuated.

16. A device according to Claim 14 or 15, wherein said removable locking member comprises a laminar member inserted between said cover and said housing.

17. A device according to any preceding claim, wherein the surface of the housing from which the needle extends or the surface of the displaceable cover, if present, is of concave cross-section, such that when the device has been applied to the skin of a subject removal of the device is resisted because the cover conforms more closely to the skin.

18. A device according to any preceding claim, modified such that the needle extending from the lower surface of the housing is replaced by a tube extending from the housing, said tube being adapted to carry a drug delivery needle thereon.

5 19. A device according to any preceding claim, wherein the reservoir is separated from the expandable chamber by a diaphragm which exhibits bistable behaviour, such that in one stable state the reservoir is full and in the other stable state the reservoir is empty, the diaphragm being shaped to minimise the energy required in the
10 transition between said stable states.

20. A device according to Claim 19, wherein the diaphragm is in the form of a body having a peripheral lip connected to a substantially flat central section by a flexible annular section, said flexible annular section assuming a substantially frusto-conical cross-
15 section in one of said states and assuming an arcuate curved cross-section in the other of said states.

21. A device according to any preceding claim, wherein the means for providing a gas comprises an electrical circuit in which any transistors are bipolar transistors having a gain of not less than 500,
20 such that said circuit can be irradiated by ionising radiation without destroying the circuit.

22. A device according to Claim 21, wherein the current gain of the or each transistor is not less than 750.

23. A device according to Claim 21 or 22, wherein the circuit
25 further comprises a reference component across which a fixed potential drop is measurable, said reference component being essentially unchanged by said ionising radiation.

24. A device according to Claim 23, wherein said reference component comprises a light-emitting diode.

25. A device according to Claim 24, wherein said light emitting diode employs gallium arsenide as a semiconductor.

26. A subcutaneous drug delivery kit comprising:

5 a) a device according to any preceding claim which is provided with a filling mechanism associated with the reservoir, the filling mechanism comprising means for receiving a filling adapter as defined in b), and

10 b) a filling adapter, comprising a body which is adapted to accommodate a cartridge, the body having means for engaging the adapter-receiving means of the device at one end thereof, means for receiving a cartridge at the other end thereof and transfer means for transferring a liquid from a cartridge to the filling mechanism of the device as the cartridge is emptied;

15 wherein the means for receiving the adapter provided on the device and the corresponding engaging means provided on the adapter together constitute a releasable locking mechanism which holds the adapter in place on the device once engaged, said locking mechanism being disengaged by the cartridge when the cartridge is emptied within the adapter.

20 27. A kit according to Claim 26, wherein said transfer means comprises a hollow double-ended needle, one end of which is associated with the engaging means such that it communicates with the filling mechanism when the adapter is engaged with the device, and the other end of which is associated with the cartridge receiving means such that
25 it communicates with the interior of a cartridge having a penetrable stopper when such a cartridge is received by the adapter.

30 28. A kit according to Claim 27, wherein both ends of the needle are disposed within the body of the adapter such that they are recessed from the exterior of the body when the adapter is disengaged from the device.

29. A kit according to any one of Claims 26-28, wherein the releasable locking mechanism comprises a pair of locking members provided on the adapter receiving means and the corresponding engaging means, respectively, one of said locking members being
5 movable between a locking position and a disengaging position, and said movable locking member being disposed relative to the body such that, in use, when a cartridge is emptied within the body, said movable locking member is moved from the locking position to the disengaging position under the action of the cartridge.

10 30. A kit according to Claim 29, wherein said movable locking member is resiliently biased towards the locking position.

31. A kit according to Claim 29, wherein said movable locking member is a latch which automatically locks the adapter and device to one another when engaged together.

15 32. A kit according to any one of Claims 26-31, wherein the cartridge is emptied by moving the penetrable stopper against the adapter.

33. A subcutaneous drug delivery kit comprising:

20 a) a device according to any preceding claim further comprising a filling mechanism associated with the reservoir, the filling mechanism comprising means for receiving a filling adapter as defined in b), and

25 b) a filling adapter, comprising a body which is adapted to receive a syringe, the body having means for engagement with the adapter-receiving means of the device at one end thereof, syringe-receiving means at the other end thereof and transfer means for transferring a liquid from the syringe to the filling mechanism of the device as the syringe is emptied, said transfer means comprising a conduit associated with the syringe receiving
30 means, the conduit leading to a needle which is associated with

the engagement means and is disposed within the body of the filling adapter.

34. A kit according to Claim 33, wherein the needle is disposed within the body of the filling adapter such that it is recessed from the exterior of the body when the adapter is disengaged from the device.

35. A method of filling a drug delivery device, comprising the steps of:

10 providing a drug delivery device having a drug reservoir, the reservoir being associated with a filling mechanism comprising filling adapter receiving means;

providing a filling adapter having a first end for engagement with the adapter receiving means, and a second end for receiving a syringe;

15 causing the filling adapter receiving means to receive the filling adapter;

causing the second end of the filling adapter to receive a syringe having liquid stored therein and a needle;

20 providing a conduit for communication between the liquid stored within the syringe and the first end of the filling adapter; and

emptying the syringe and concurrently transferring the liquid from the syringe to the device *via* the conduit.

36. A filling adapter as defined in any one of Claims 26-35.

37. A diaphragm as defined in Claim 19 or 20.

25 38. A subcutaneous drug delivery device, substantially as hereinbefore described with reference to and as illustrated in Figs. 1-21, 23, 24 and 25 of the accompanying drawings.

39. A subcutaneous drug delivery kit, substantially as hereinbefore described with reference to and as illustrated in Figs. 21-24 of the accompanying drawings.

5 40. A filling adapter, substantially as hereinbefore described with reference to and as illustrated in Figs. 21-24 of the accompanying drawings.

41. A diaphragm, substantially as hereinbefore described with reference to and as illustrated in Figs. 26 and 27 of the drawings.

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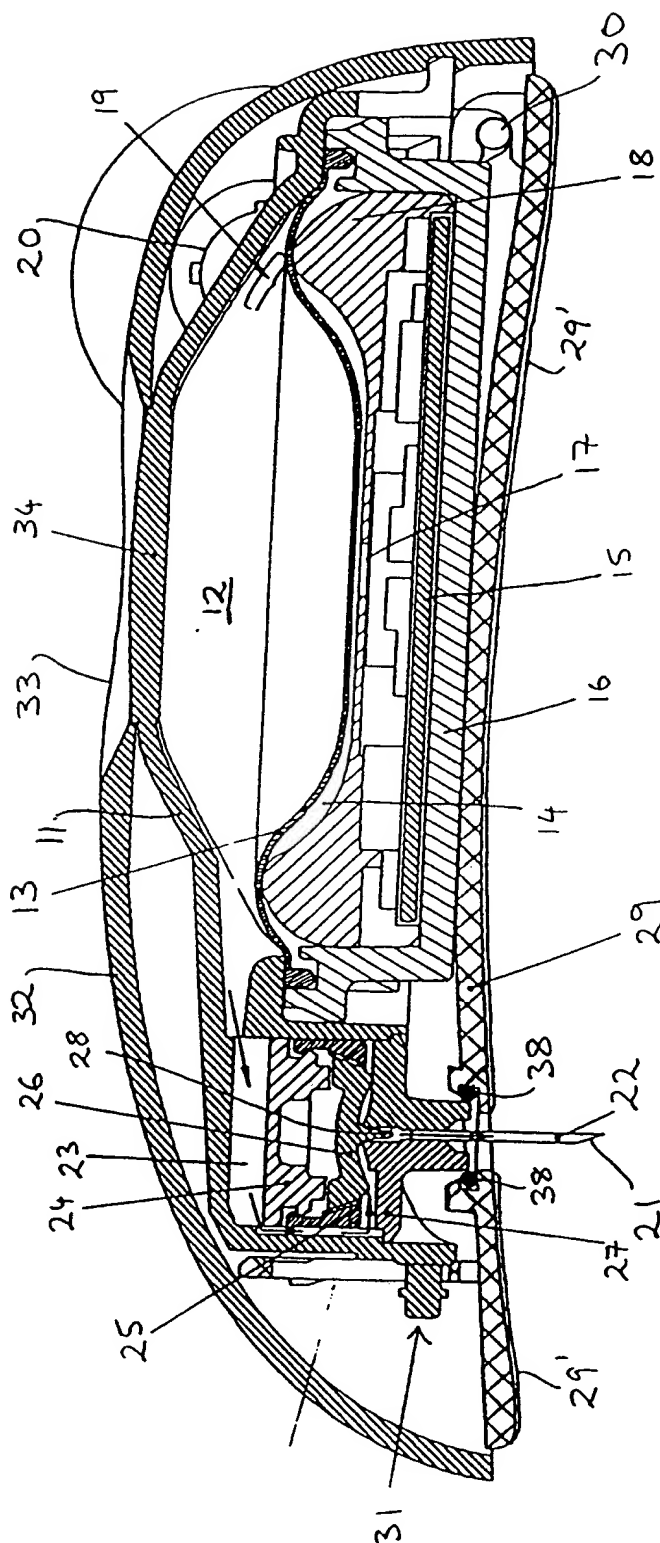
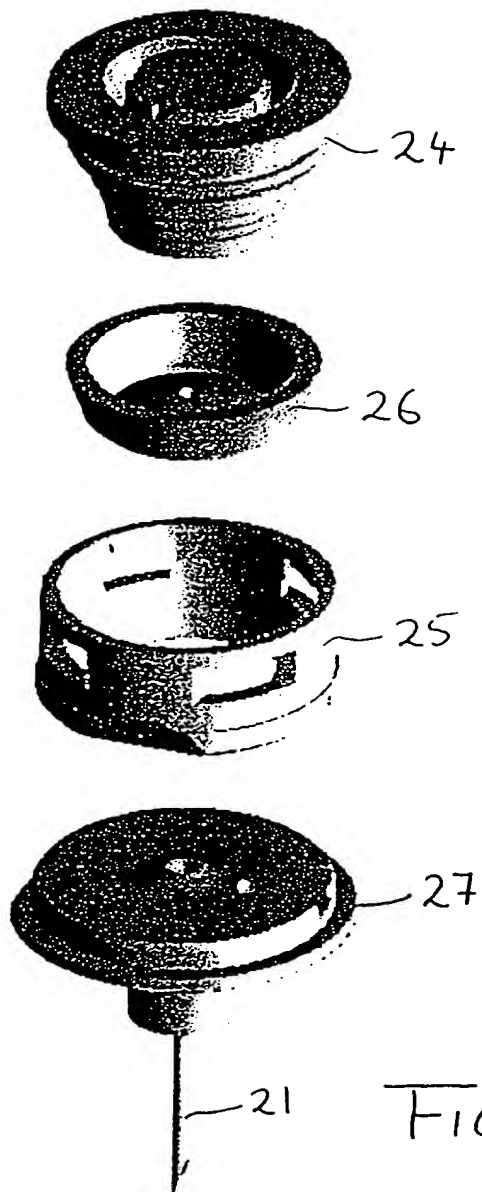


Fig. 1

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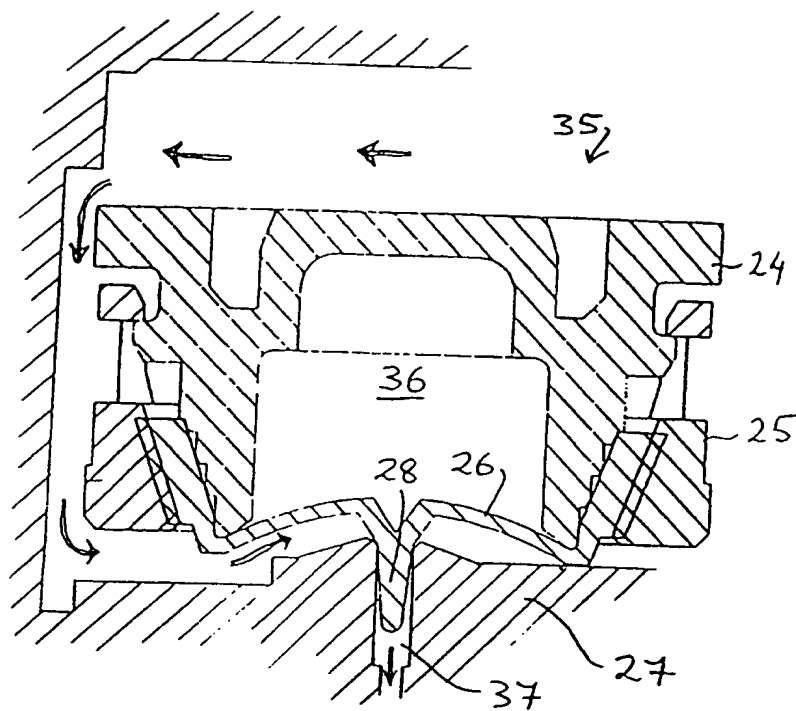


FIG. 3

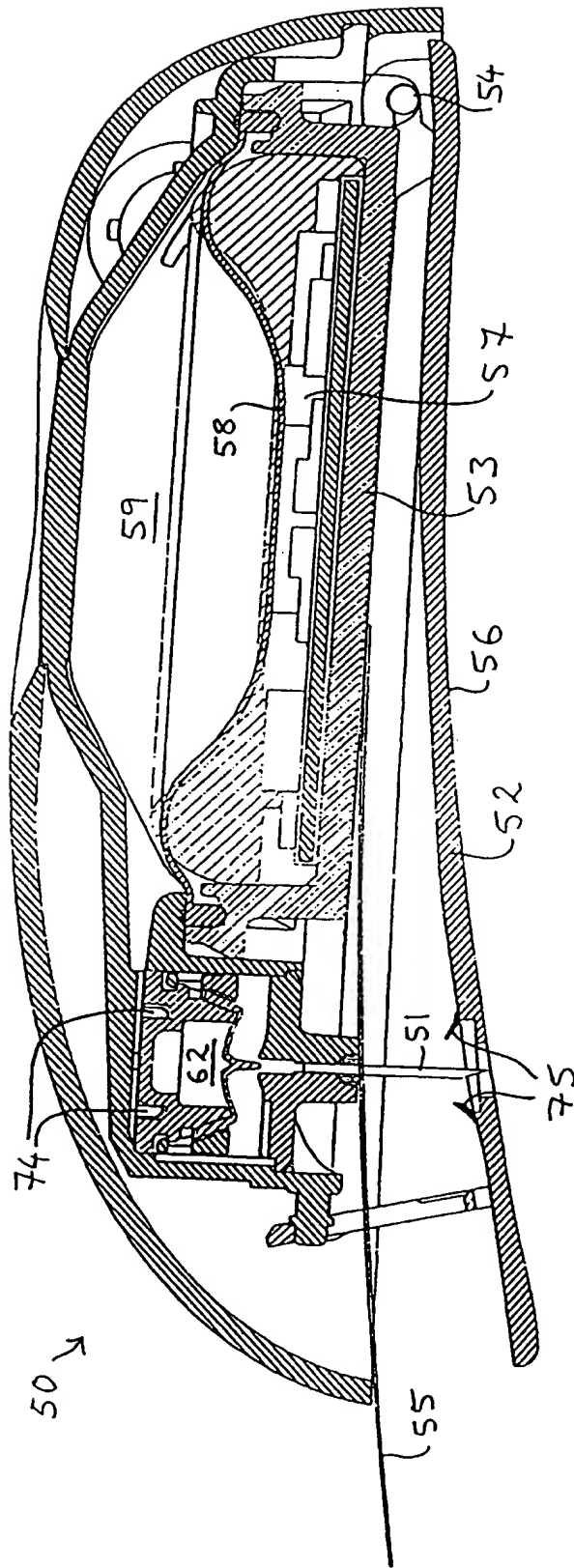
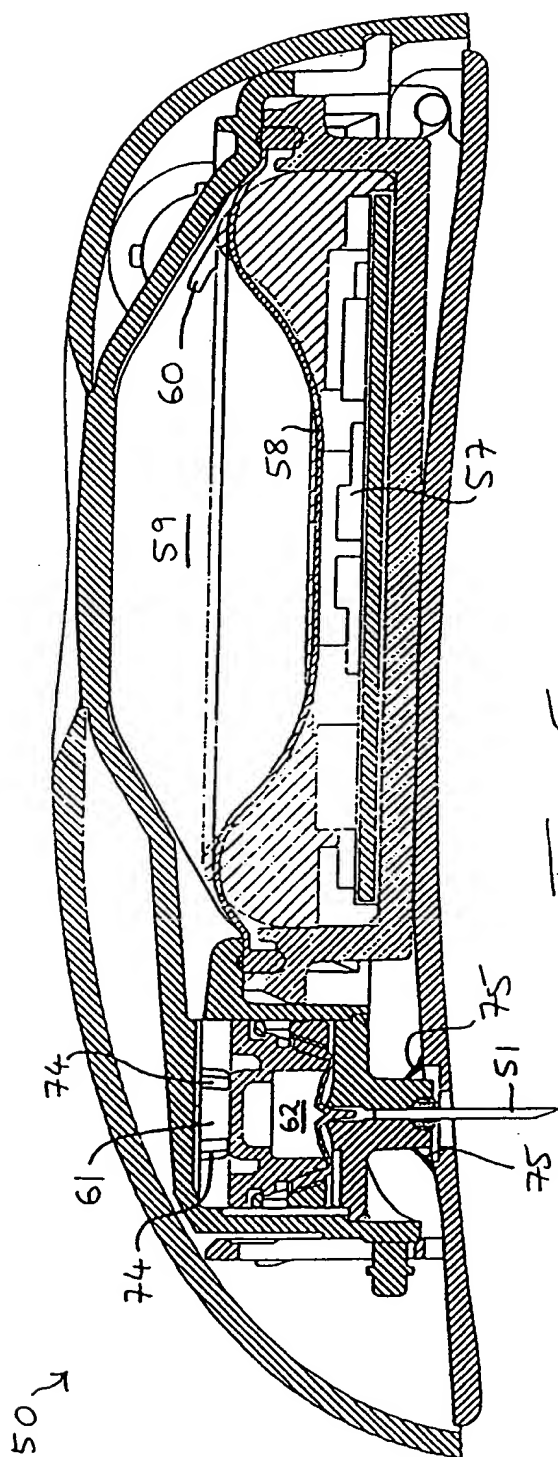
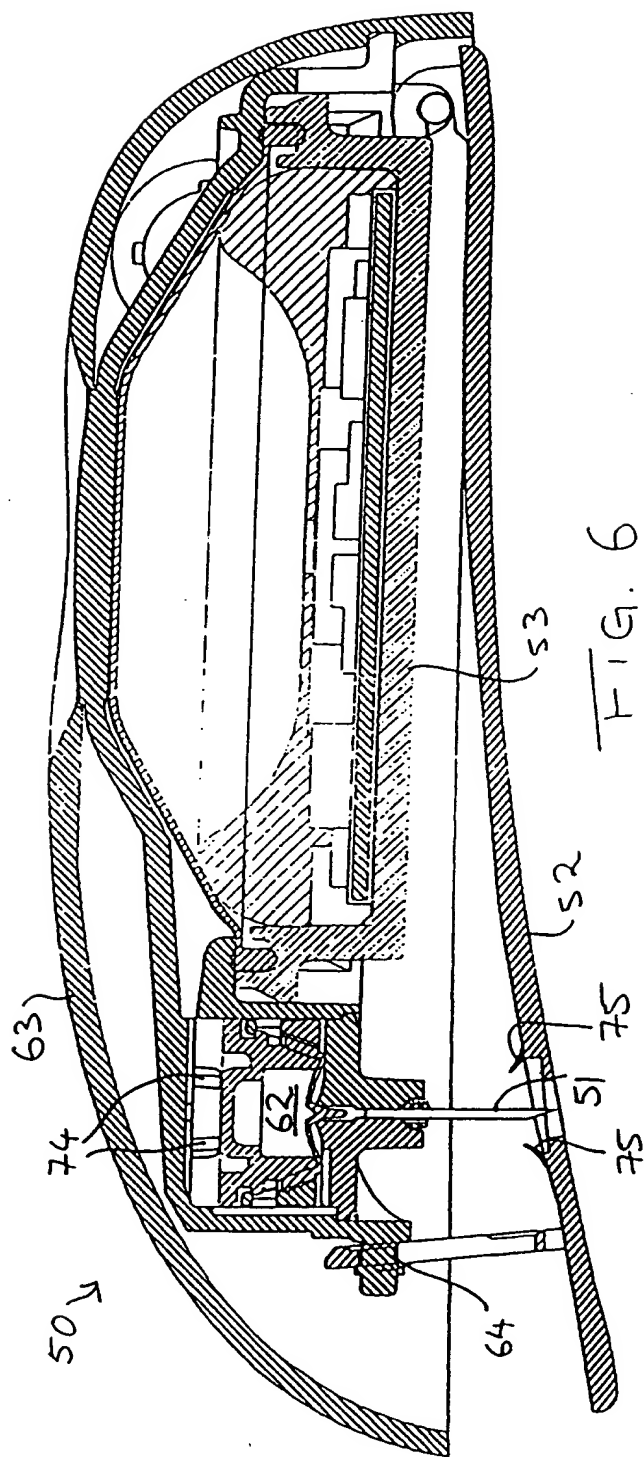


FIG 4

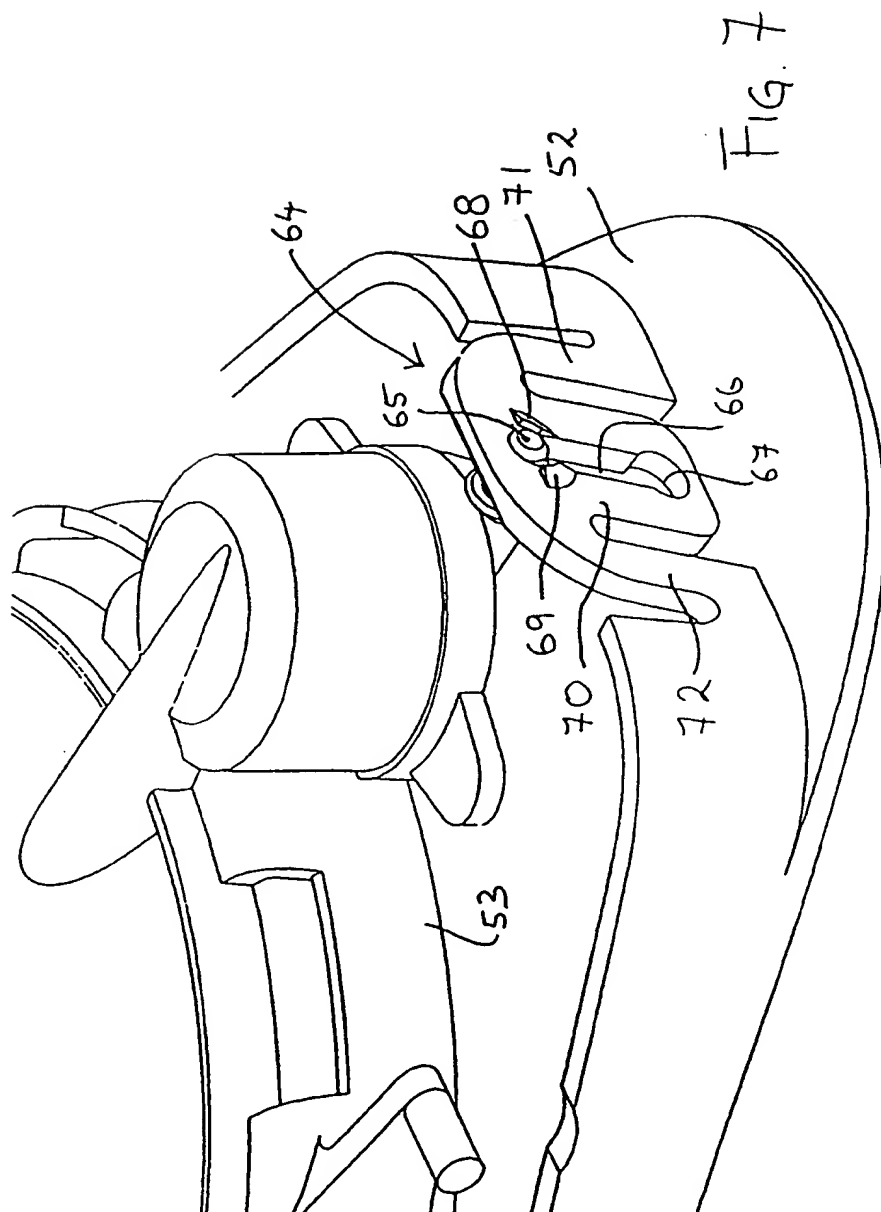


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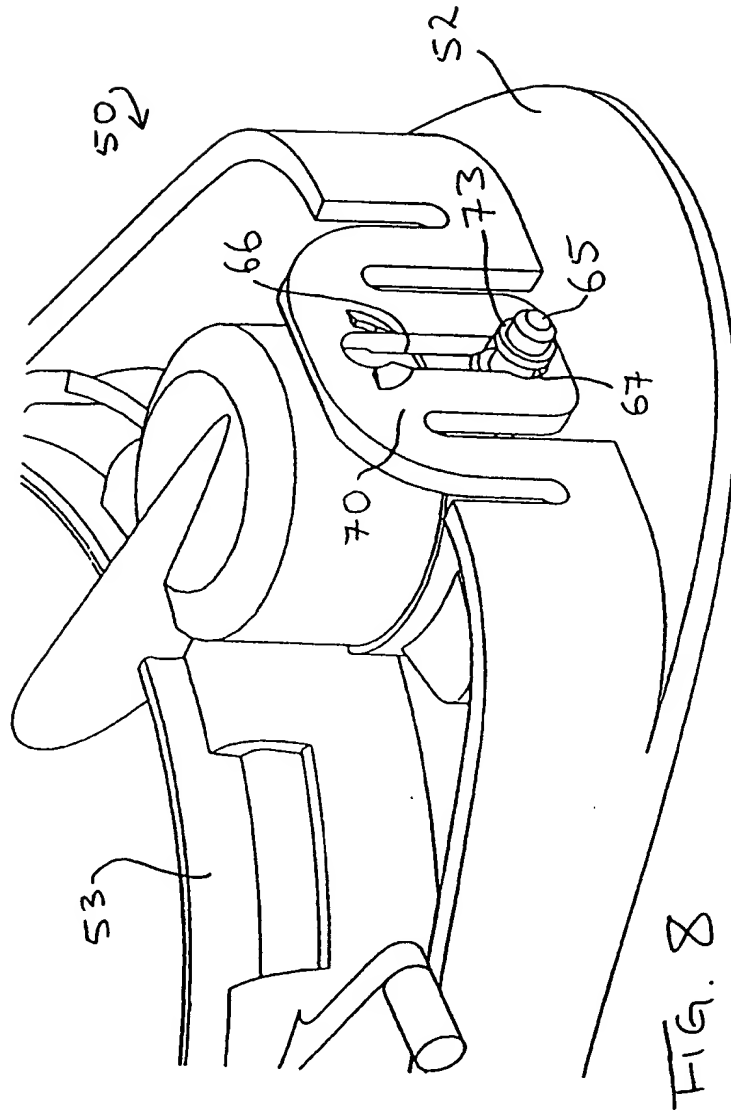
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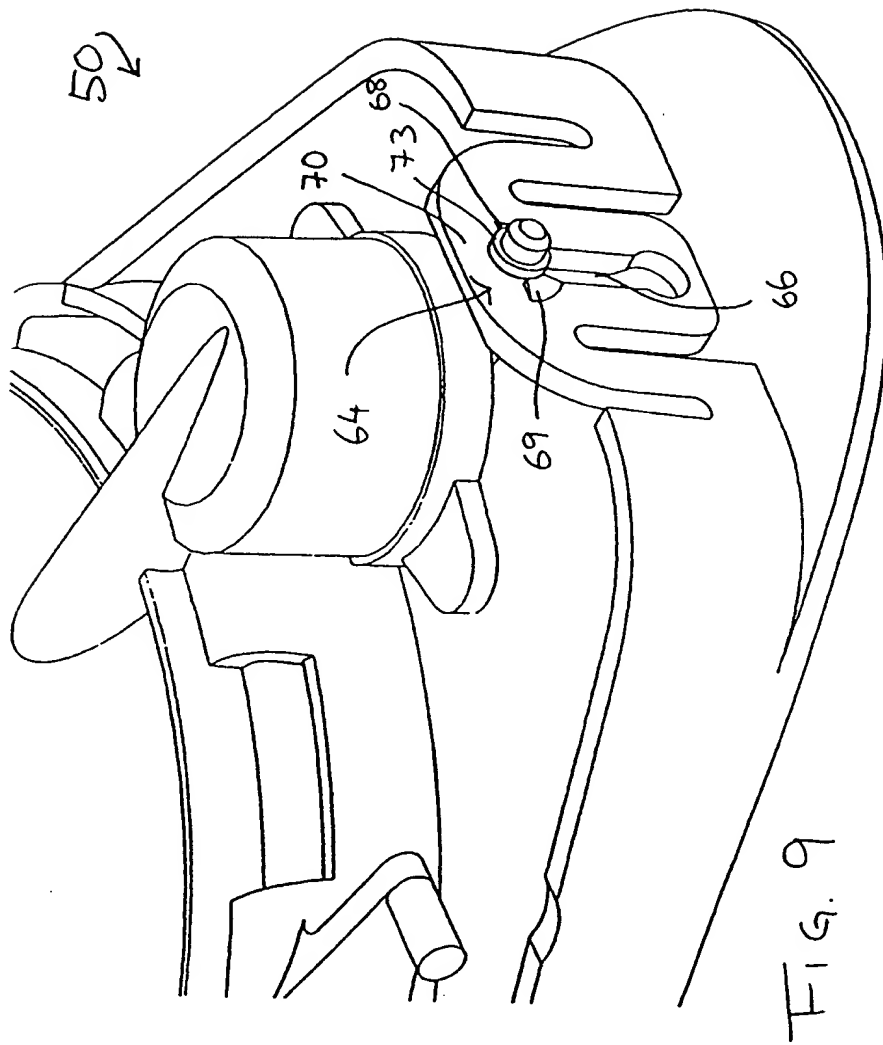
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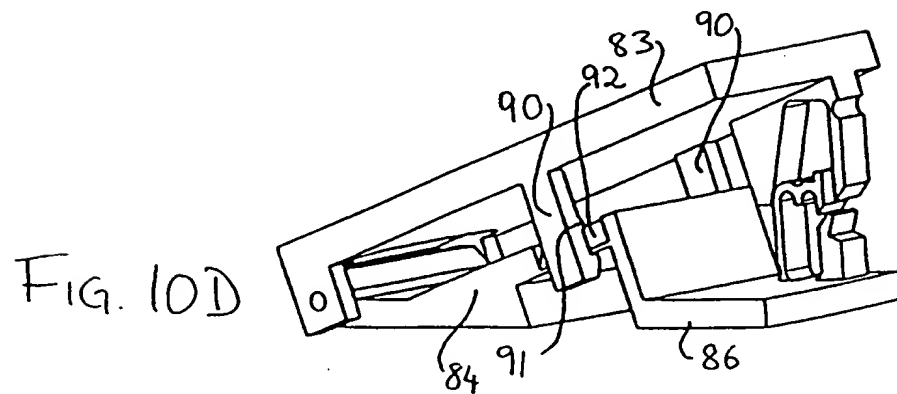
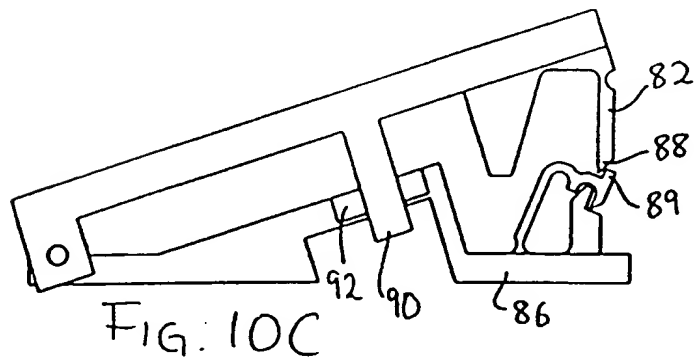
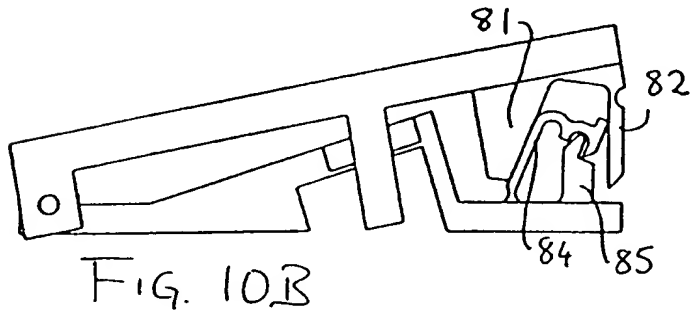
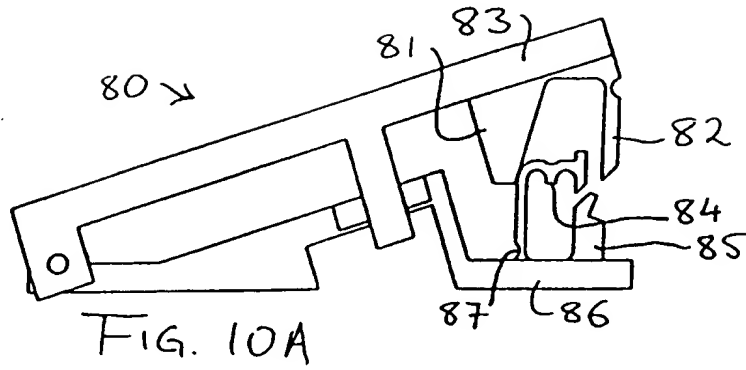
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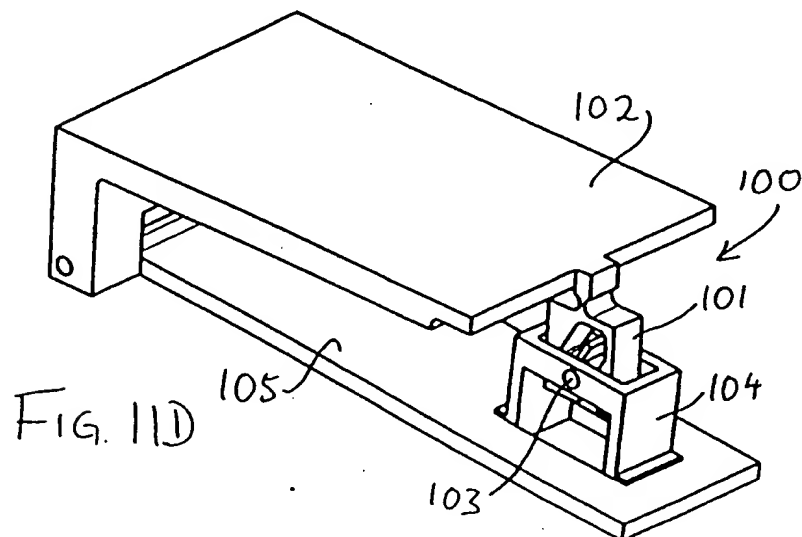
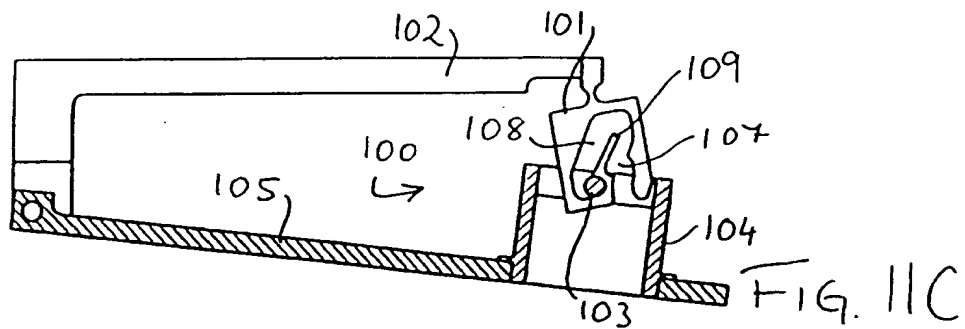
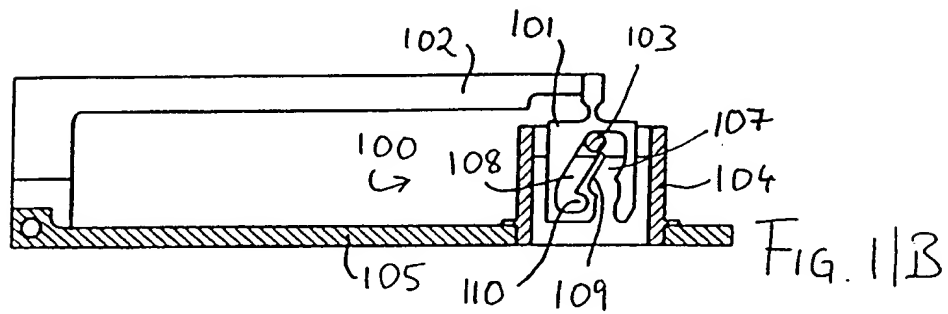
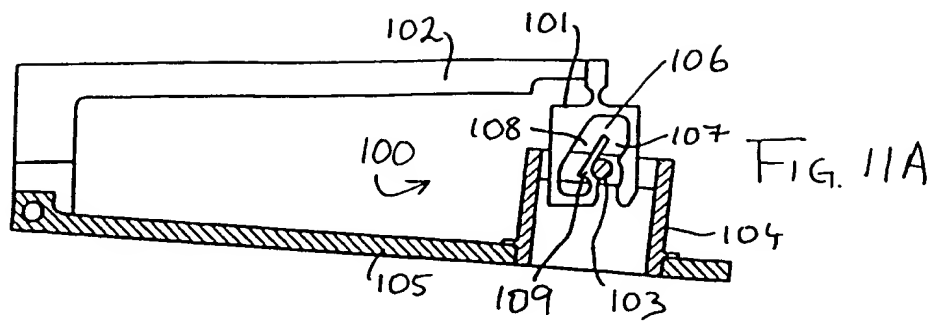
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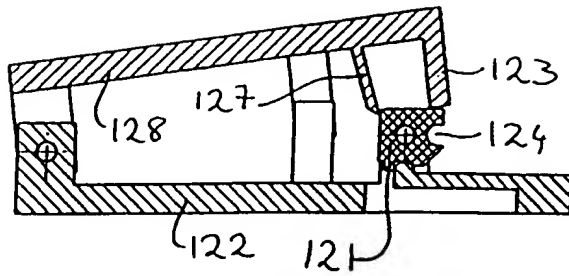


FIG. 12A

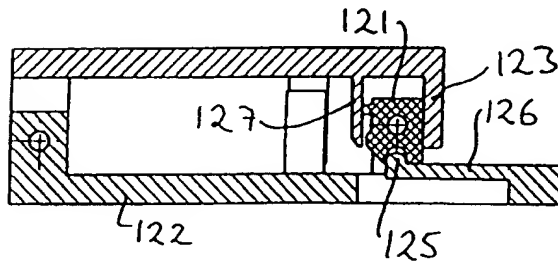


FIG. 12B

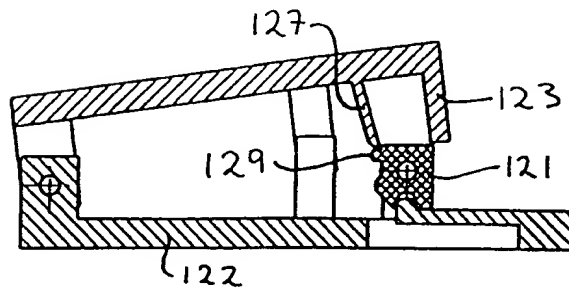


FIG. 12C

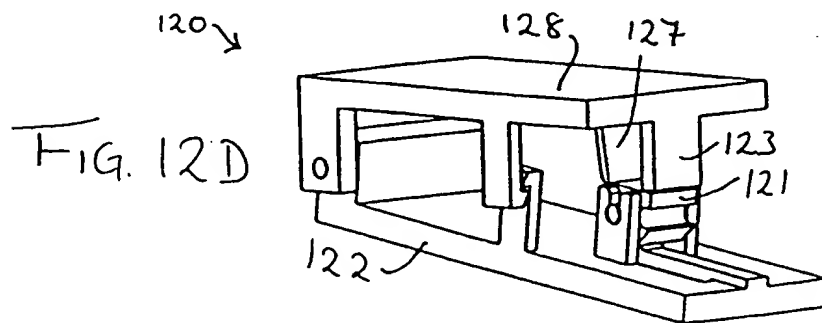
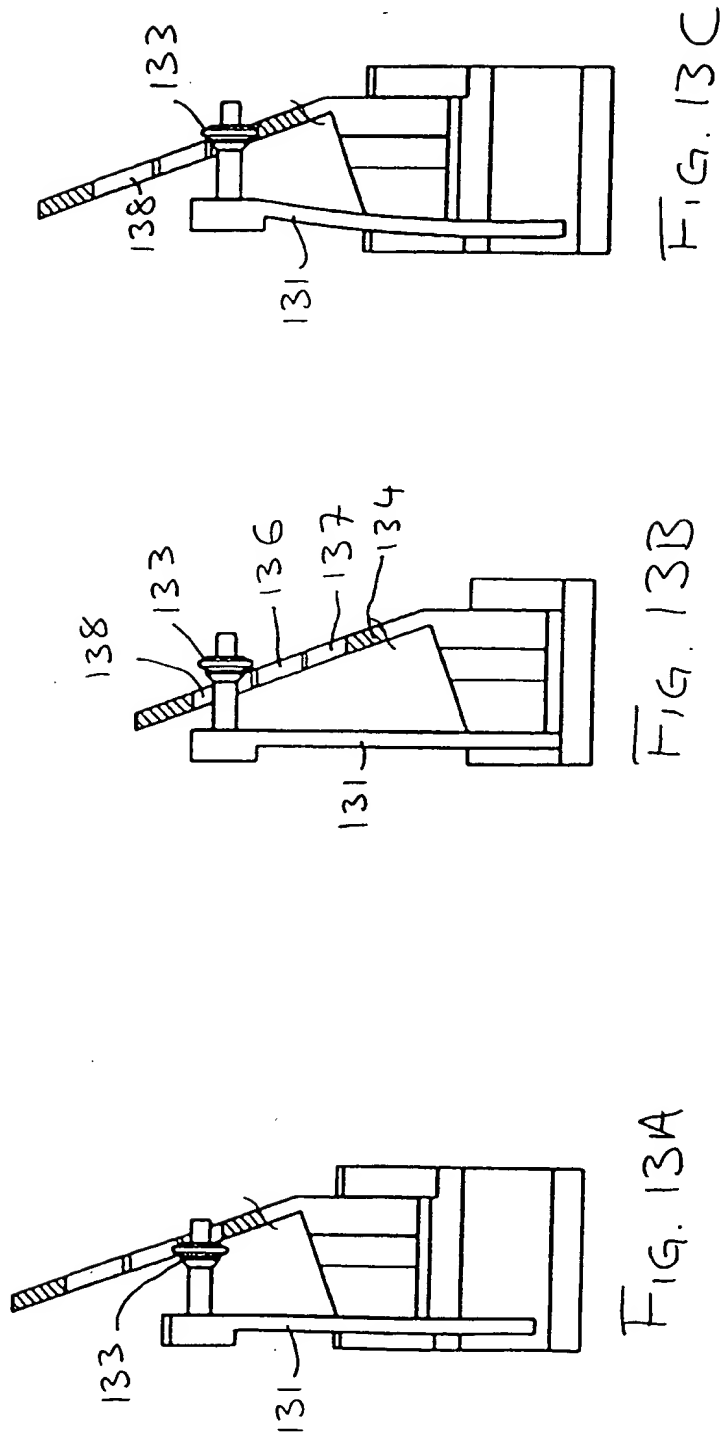


FIG. 12D

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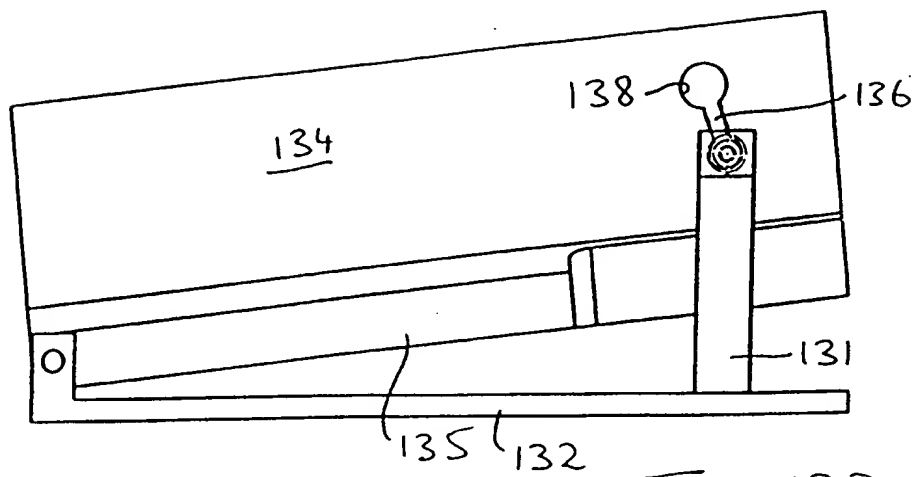


FIG. 13D

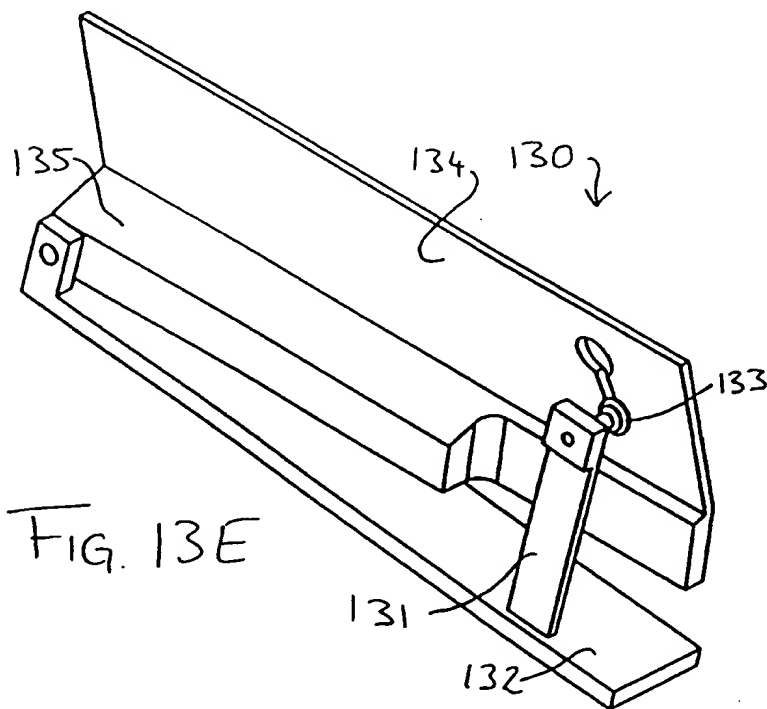


FIG. 13E

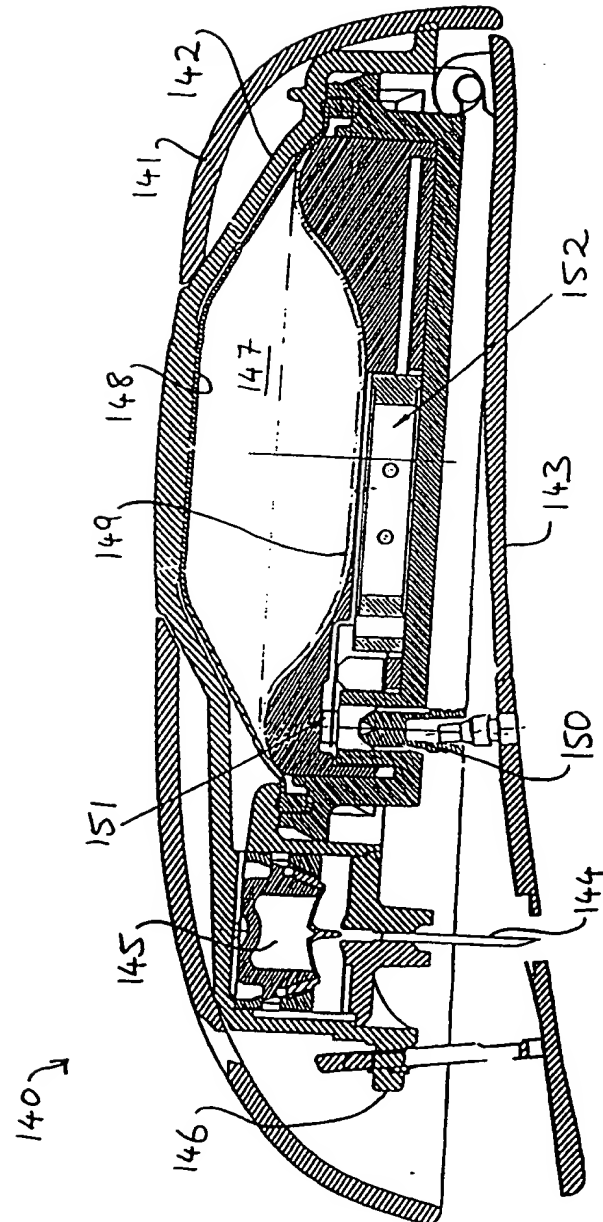


FIG. 14

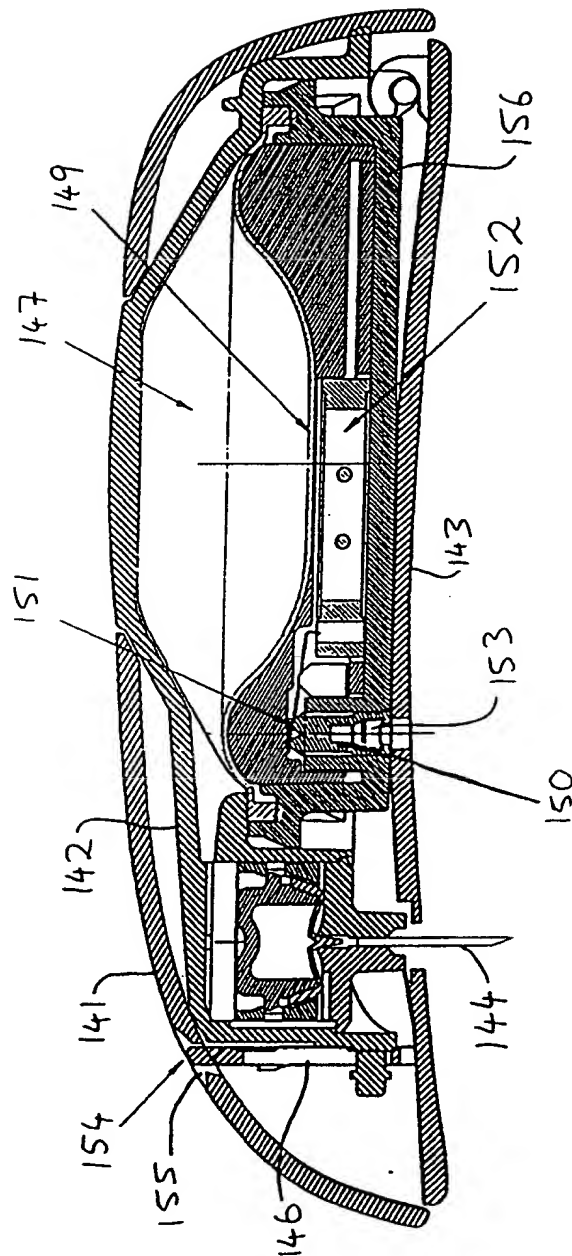
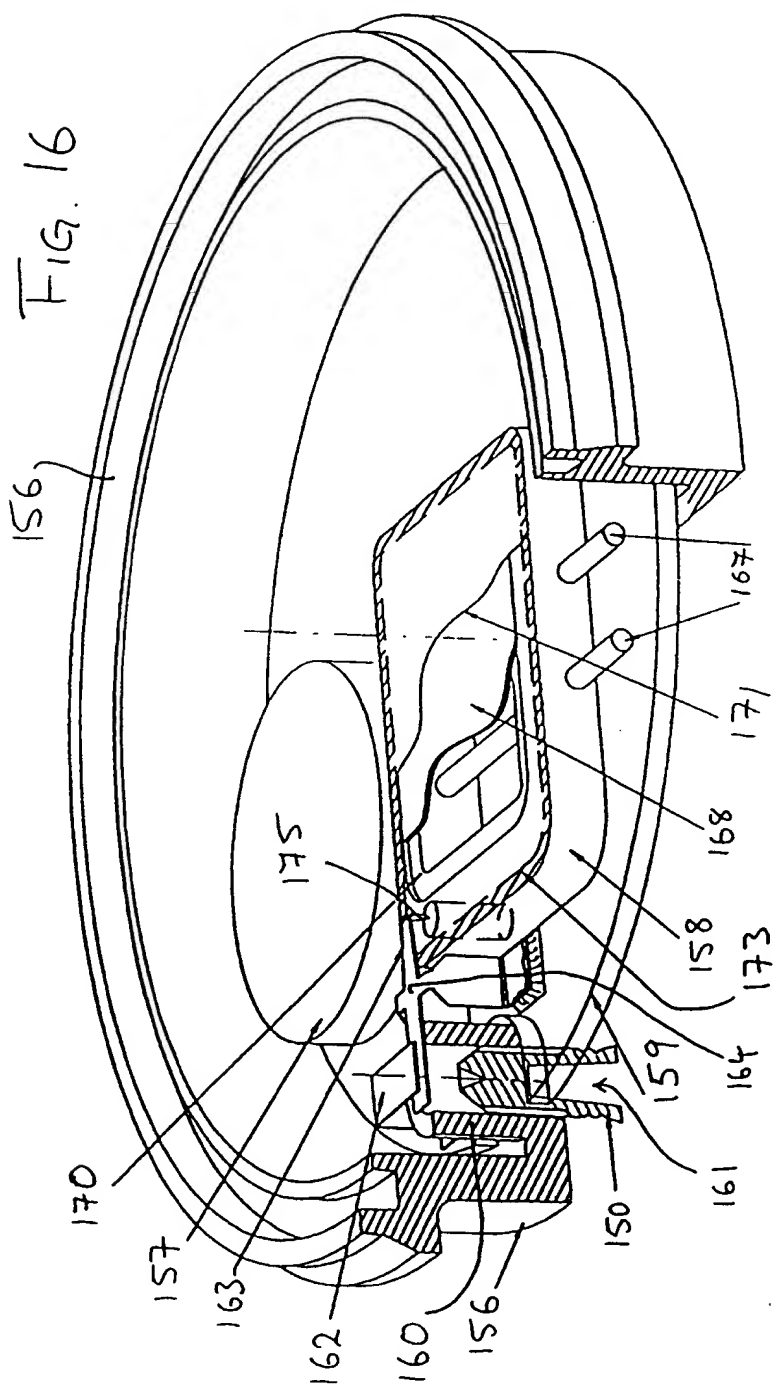


Fig. 15



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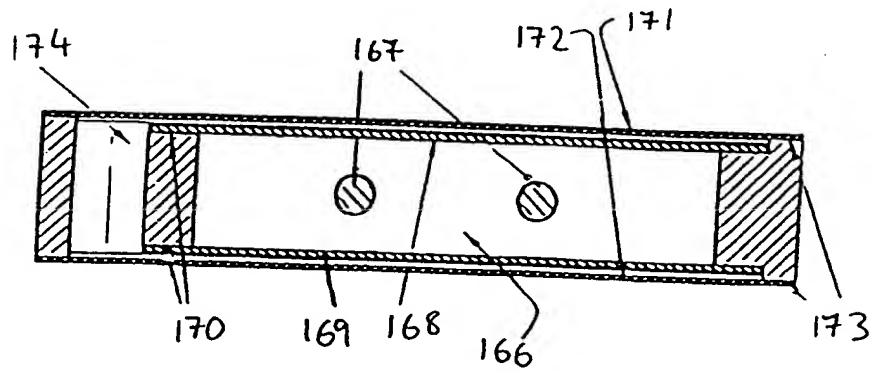
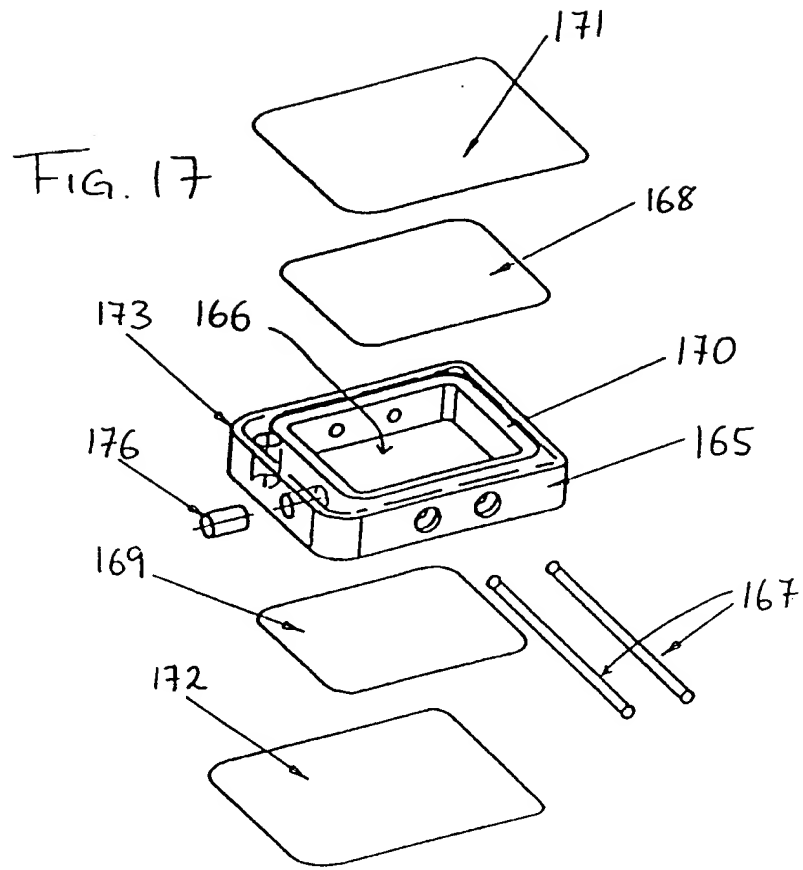


FIG. 18

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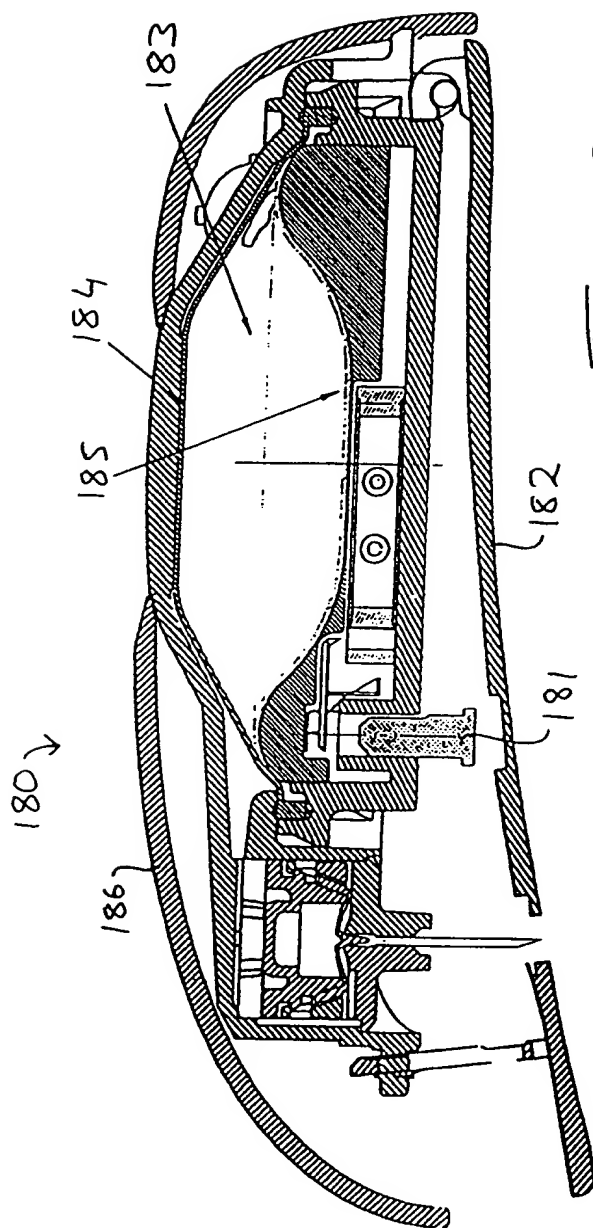


FIG. 19

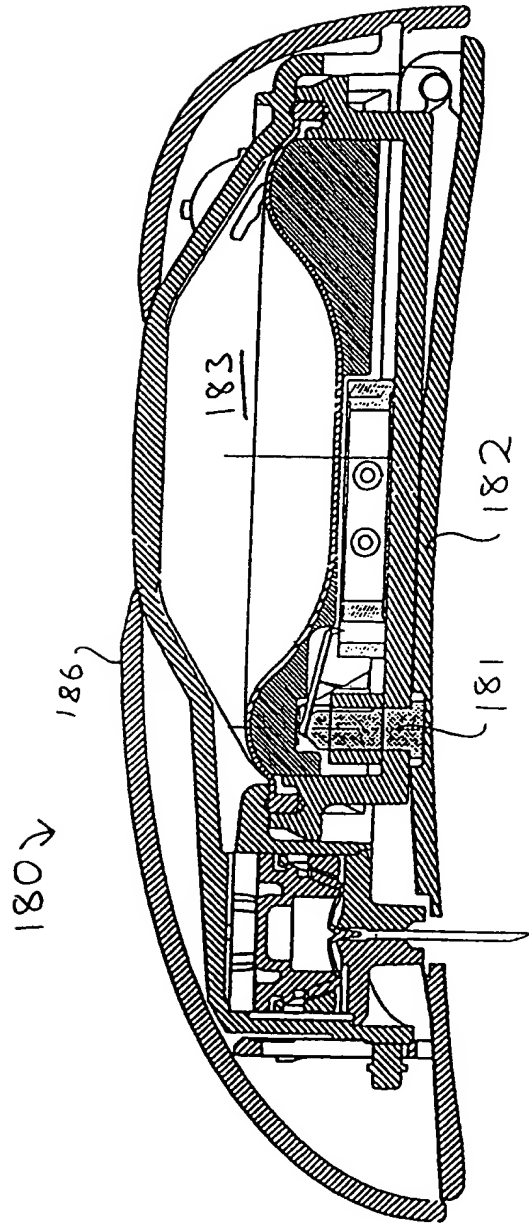
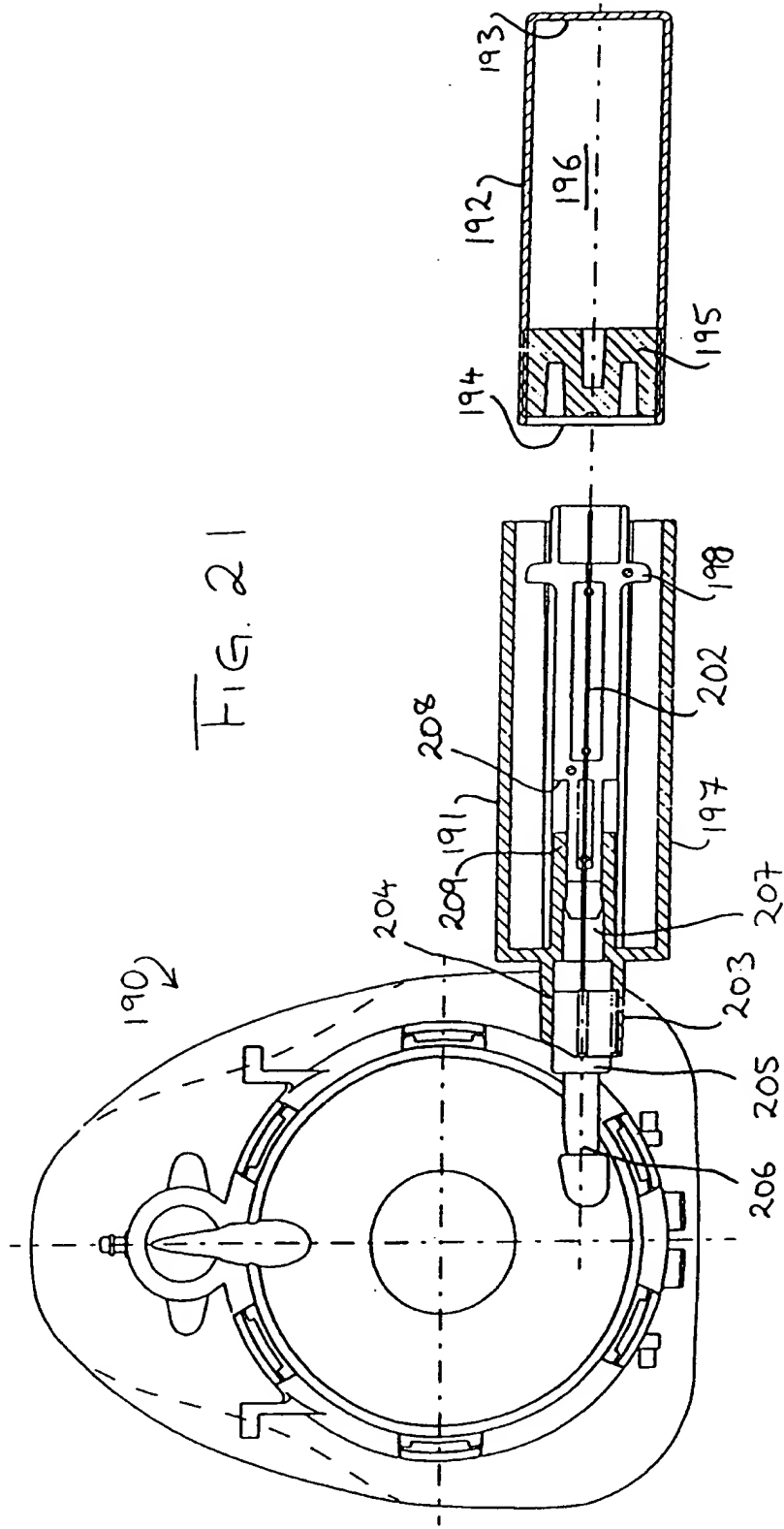


FIG. 20

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FIG. 21



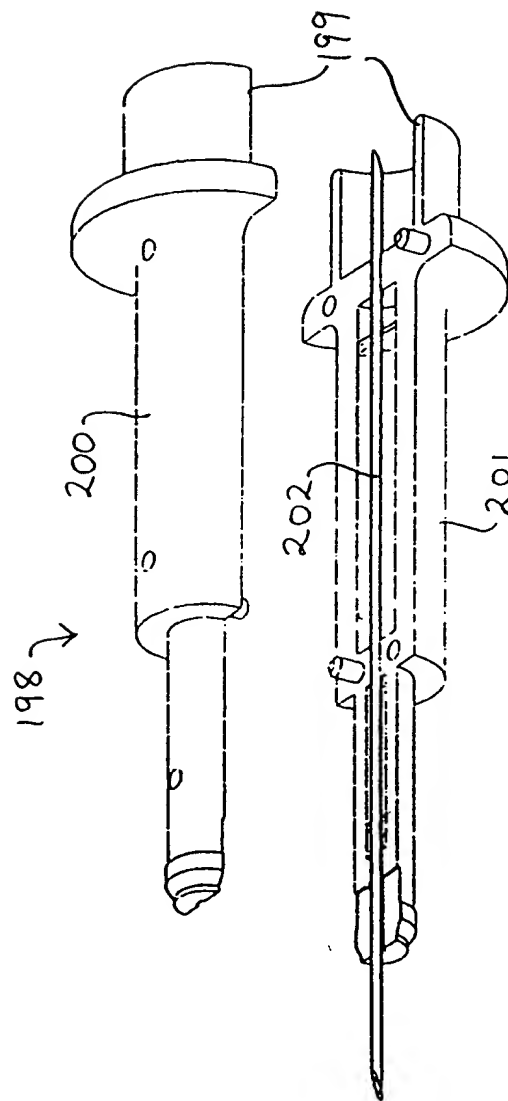


FIG. 22

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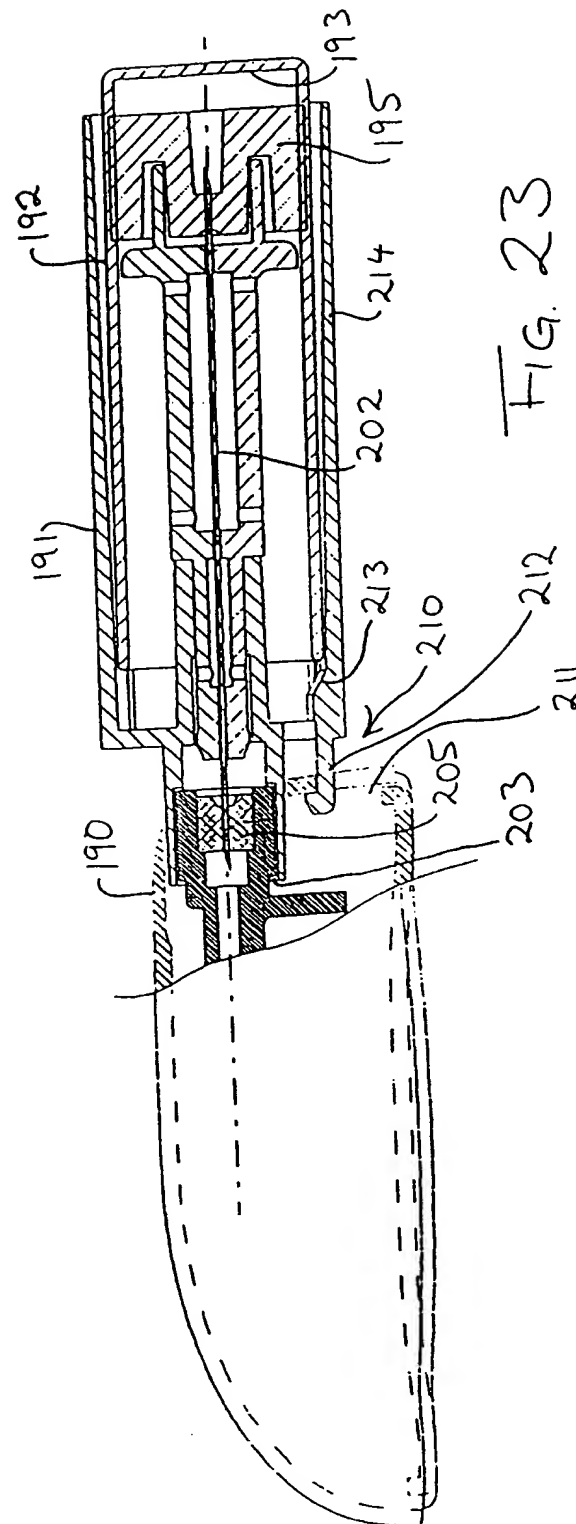
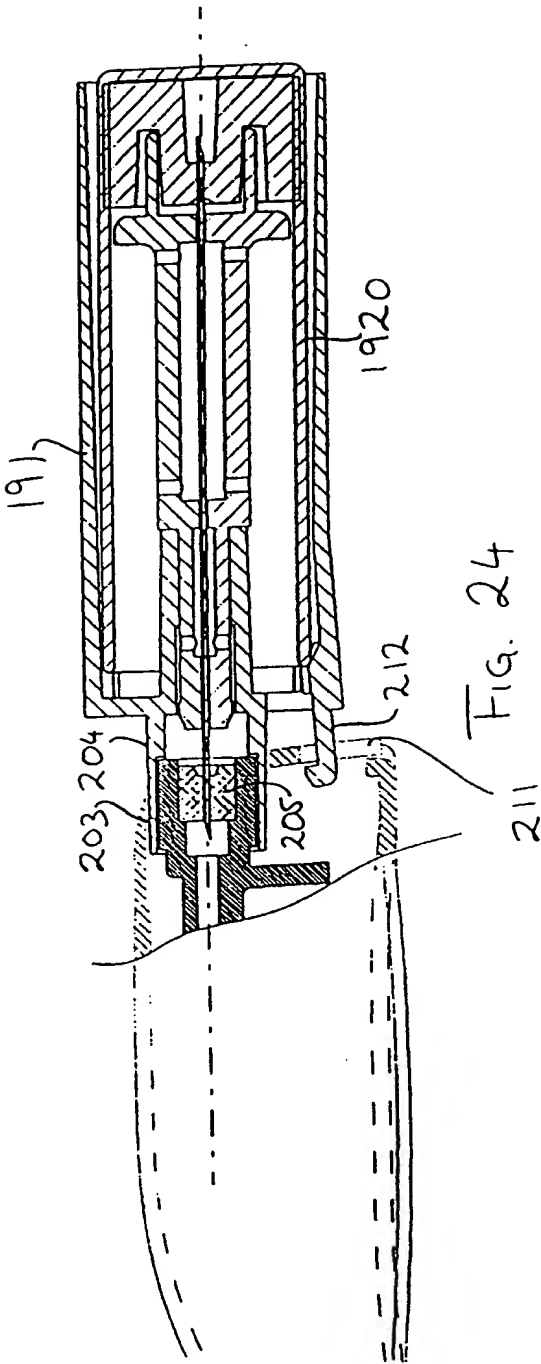
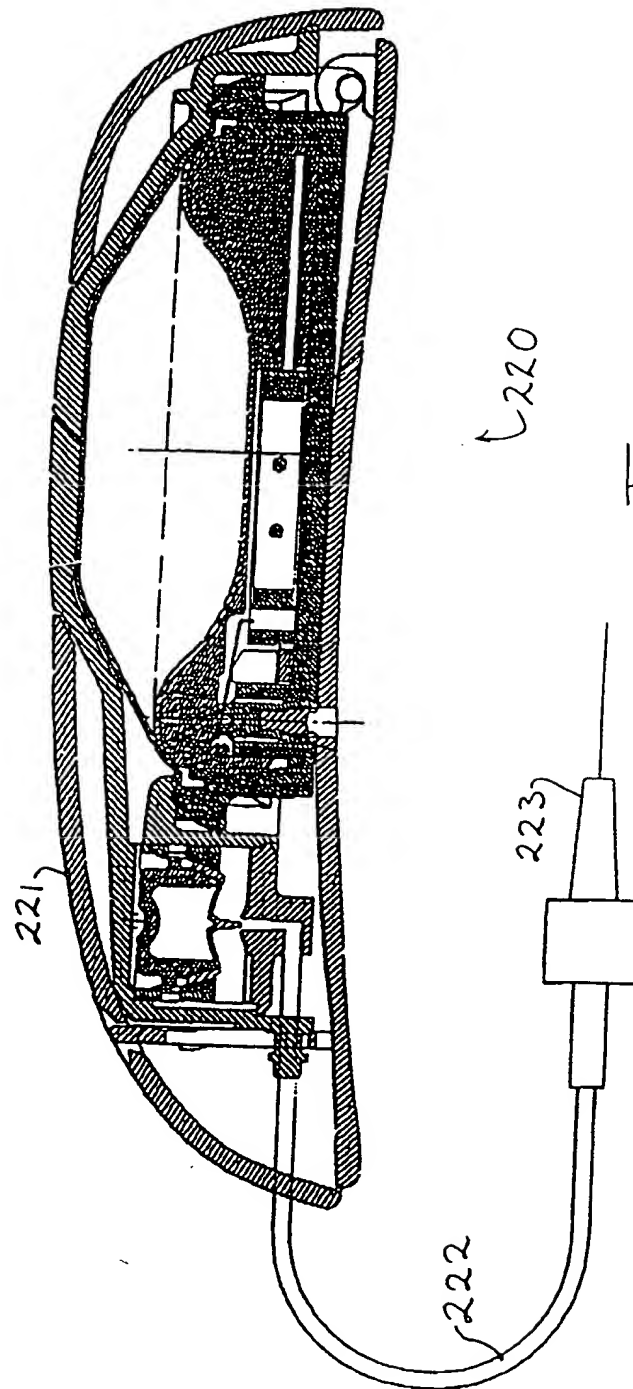


FIG. 23



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FIG. 25

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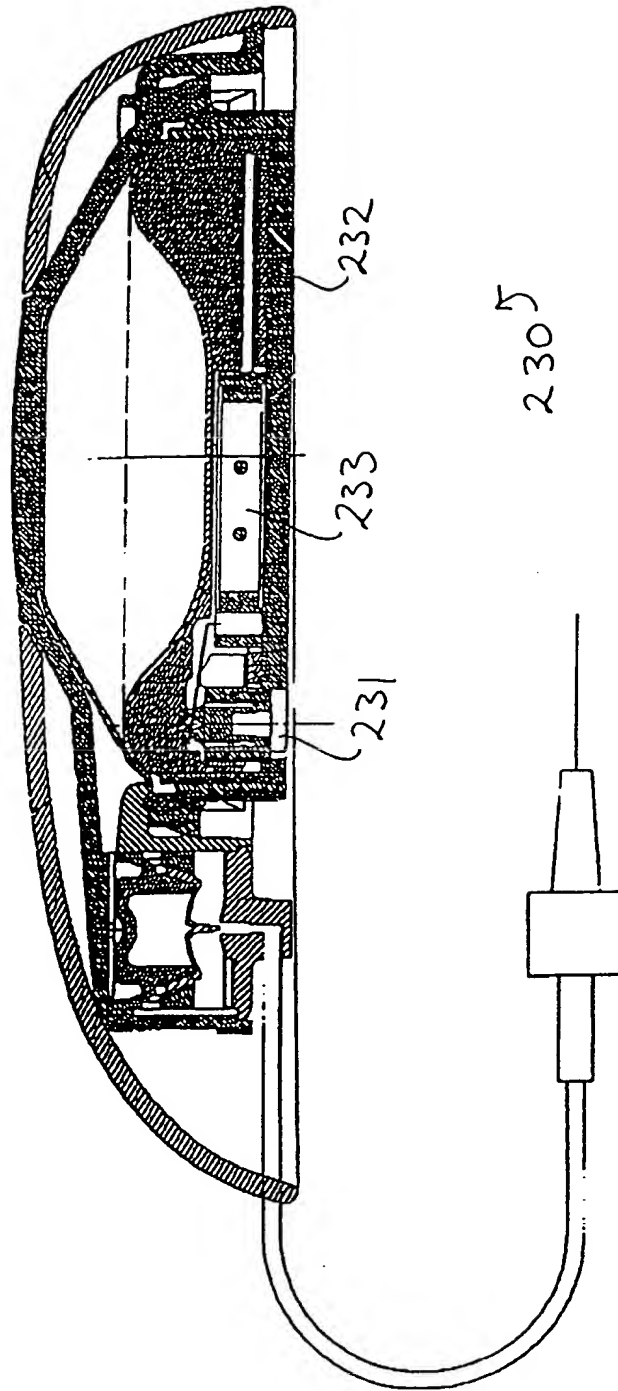
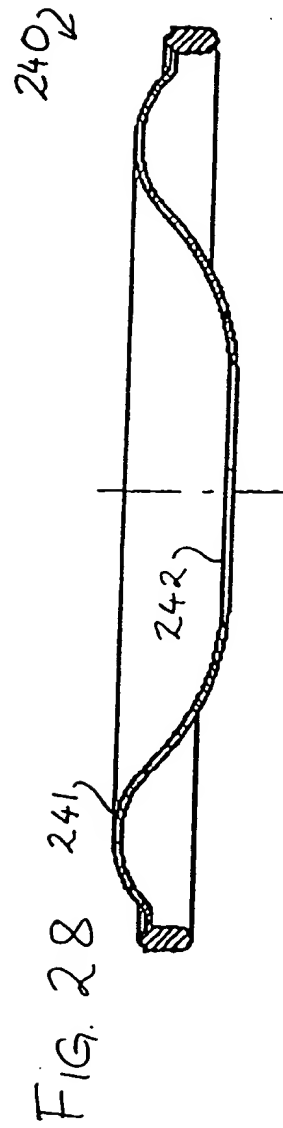
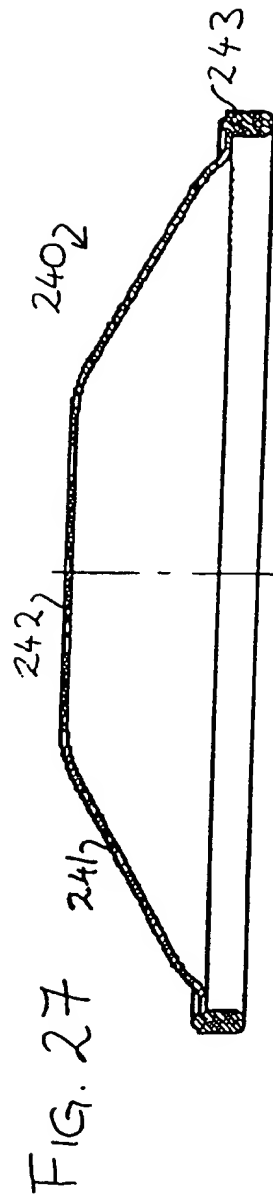


FIG. 26

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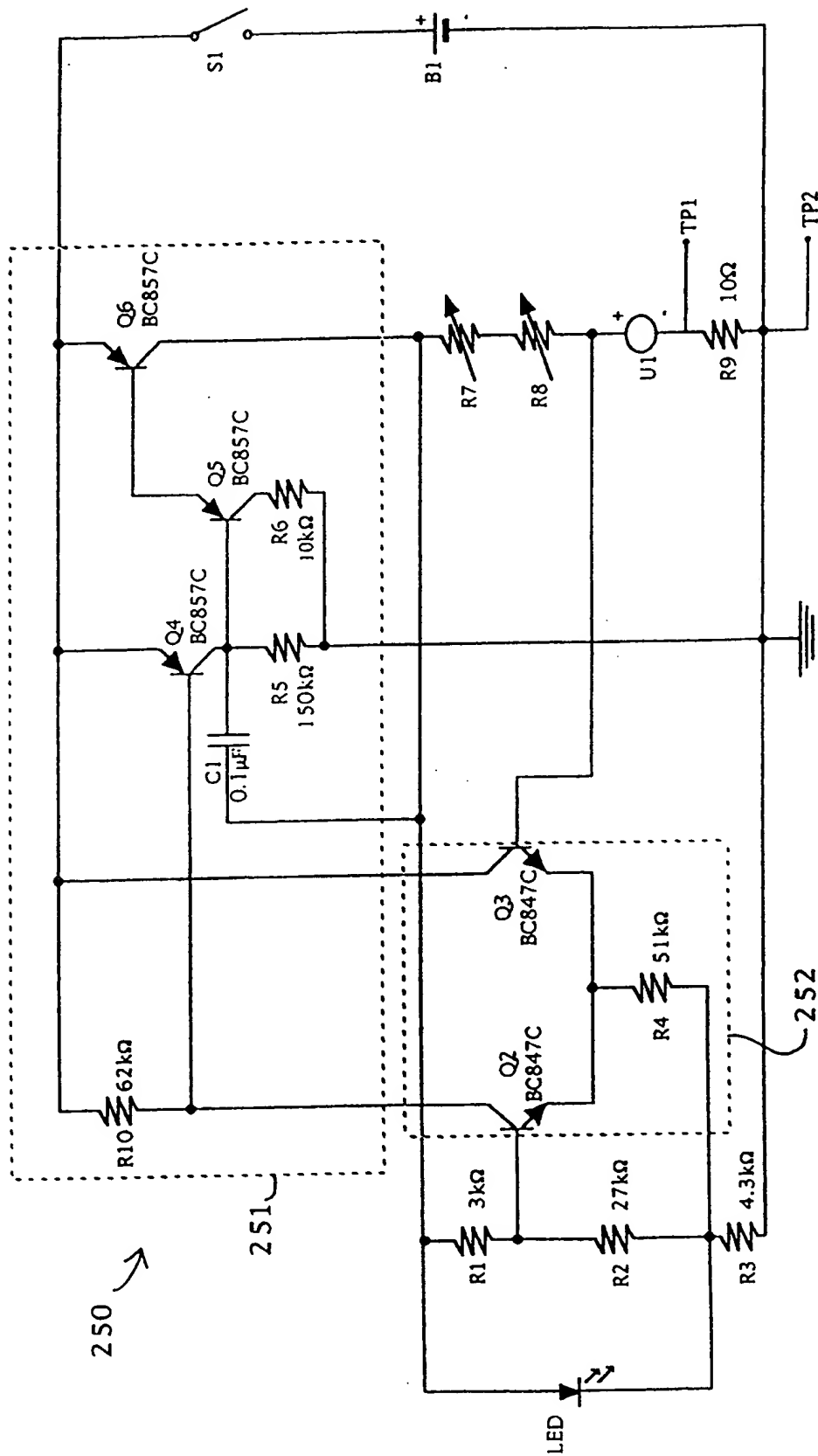
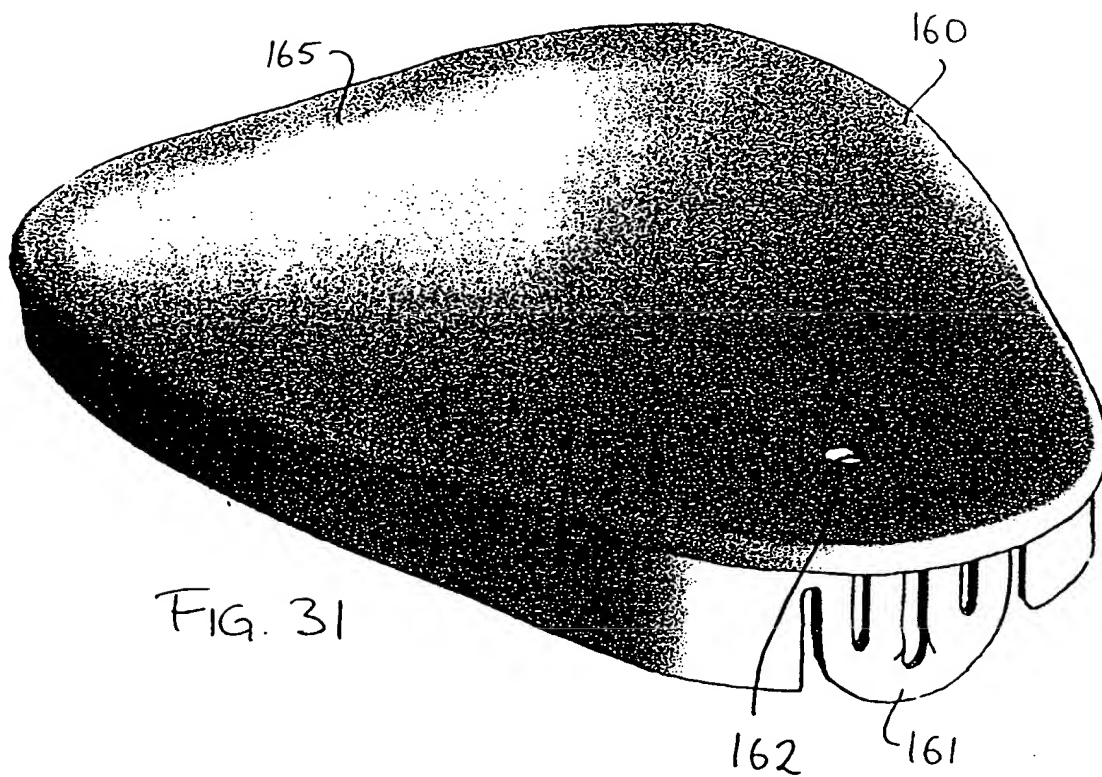
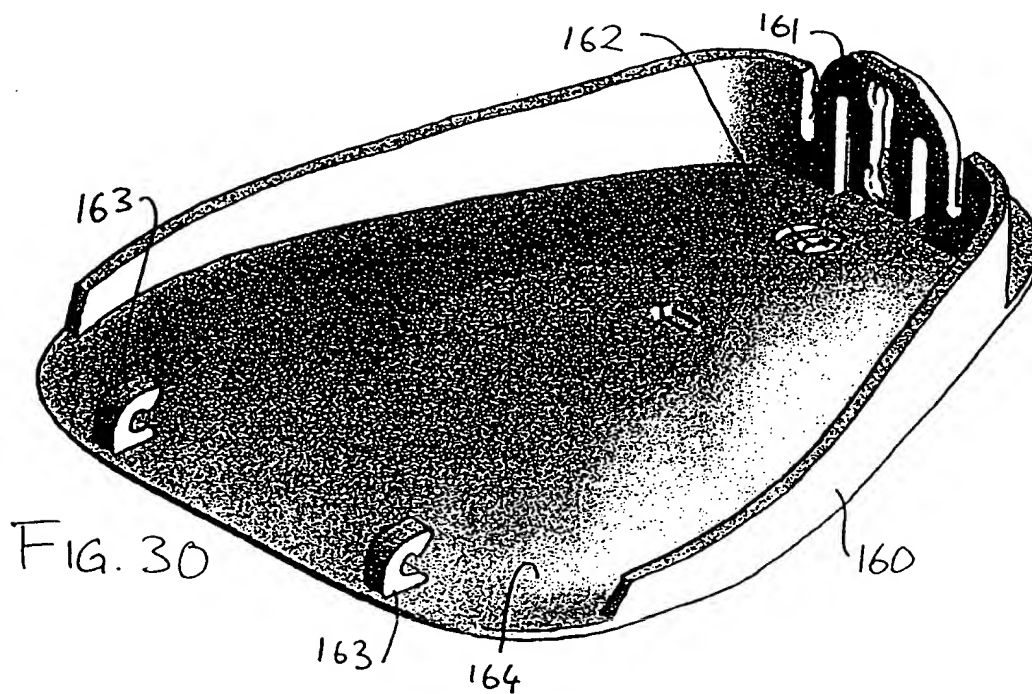


Fig. 29



INTERNATIONAL SEARCH REPORT

Inter. .nal Application No

PCT/IE 98/00042

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M5/168 A61M5/145

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 32013 A (ELAN MED TECH ;GROSS JOSEPH (IE); KELLY JOHN GERARD (IE)) 30 November 1995 see claims 1,2; figures see page 11, line 24 - line 28 ---	1-6, 18, 19, 37
X	US 4 886 499 A (CIRELLI GIORGIO ET AL) 12 December 1989 see column 2, line 35 - line 41 see column 5, line 3 - line 25 see column 5, line 26 - line 59; figures ---	1-7, 14, 18, 19, 37
X	EP 0 494 042 A (SCIENT INNOVATIONS LTD) 8 July 1992 see the whole document ---	1-6, 18-20, 37
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

26 May 1999

Date of mailing of the international search report

07. 06. 1999

Name and mailing address of the ISA

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Authorized officer

Clarkson, P

INTERNATIONAL SEARCH REPORT

Int. onal Application No

PCT/IE 98/00042

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 03078 A (ELAN MED TECH ;GROSS JOSEPH (IE)) 2 February 1995 see page 14, line 3 - line 13; claim 1; figures ---	1,2,18, 19,37
X	WO 97 10012 A (ELAN MED TECH ;GROSS JOSEPH (IE)) 20 March 1997 cited in the application A see the whole document ---	1,7, 19-22,37 2-6, 8-18, 23-36
X	EP 0 258 073 A (PISTOR MICHEL) 2 March 1988 see figures 8 and 9 and the related description ---	1,19,20
X	WO 95 13838 A (ELAN MED TECH ;GROSS JOSEPH (IE); KELLY JOHN GERARD (IE)) 26 May 1995 cited in the application A see the whole document ---	1,7 2-6,8-37
X	WO 97 41917 A (CERAMATEC INC) 13 November 1997 see example I ---	1,7, 21-23
X	WO 97 13544 A (SCIENCE INC) 17 April 1997 see page 16, paragraph 3; figures ---	1,17, 33-36
X	US 5 318 540 A (ATHAYDE AMULYA L ET AL) 7 June 1994 see figure 2 ---	1,18, 21-23
X	US 5 411 480 A (KRIESEL) 2 May 1995 see column 22, line 62 - column 23, line 19; figures 43,44 -----	1,35,36

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IE 98/00042

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 38-41
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
The features of the claims are not defined (Rule 6.2(a) PCT). For this reason, a meaningful search in the sense of Article 17(2)(a)(ii) PCT cannot be carried out and no international search is established with respect to these claims.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ IE 98/00042

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-6 18

A gas driven drug delivery device with a flow regulating chamber which varies the flow resistance between reservoir and outlet.

2. Claims: 1,7-16

A gas driven drug delivery device with a flow regulating chamber having a displaceable cover to cause needle penetration.

3. Claims: 1,17

A gas driven drug delivery device with a flow regulating chamber having a surface of concave section for application to the skin.

4. Claims: 1,19,20,37

A gas driven drug delivery device with a flow regulating chamber and a diaphragm exhibiting bistable behaviour.

5. Claims: 1,21-25

A gas driven drug delivery device with a flow regulating chamber wherein the means for supplying gas is an electrical circuit.

6. Claims: 1,26-34

A kit comprising a gas driven drug delivery device with a flow regulating chamber and a filling adapter.

7. Claims: 35,36

A method of filling a drug delivery device involving use of a filling adapter and a filling adapter.

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